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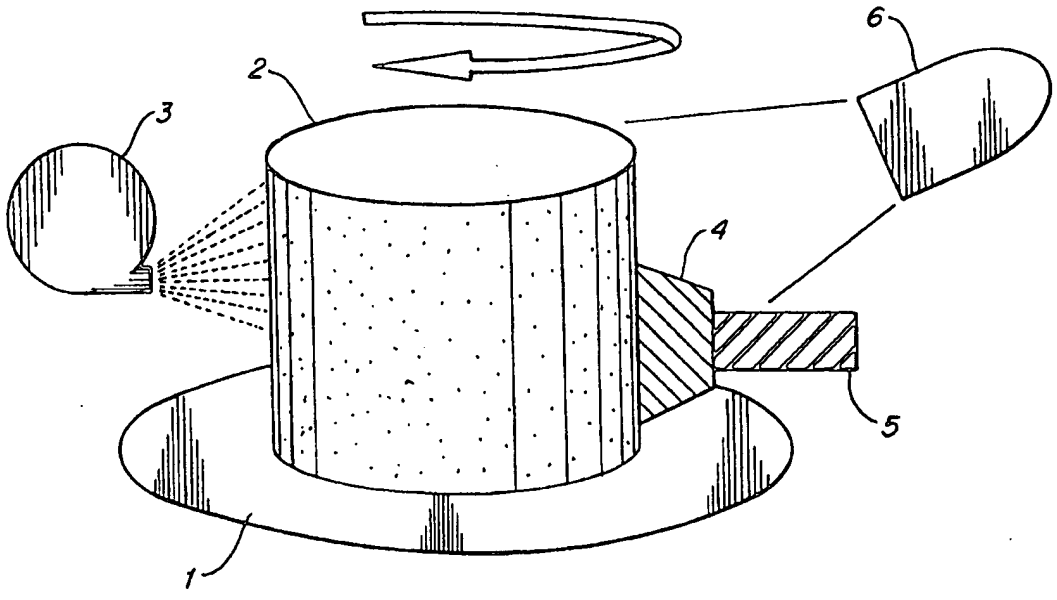

(57) Abstract

Flakes containing drugs and methods for forming and using such flakes are provided.

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ORAL DELIVERY FORMULATION

Related Applications

This application claims the benefit of priority under 35 U.S.C. Section 119 to U.S. patent application entitled "Oral Delivery Formulation", filed December 15, 1997, Serial No. 60/069501, U.S. patent application entitled "Oral Delivery Formulation", filed February 4, 1998, Serial No. 60/073867, and under 35 U.S.C. §120 to U.S. Patent Application entitled "Oral Delivery Formulation", filed April 4, 1998, Serial No. 09/055,163 and U.S. Patent Application entitled "Oral Delivery Formulation", filed April 6, 1998, Serial No. 09/055,569.

Background of the Invention

Current orally delivered drugs are formulated in either solid (i.e., tablet, capsule or granules) or liquid (i.e., solution, suspension or emulsion) form. Solid dosage forms are conventionally the dosage of choice as they are typically more stable, less expensive to manufacture and have achieved general acceptance by consumers. The manufacture of solid dosage forms typically involves the processing of the drug with suitable excipients in order to produce a freely-flowing powder. The type of processing and excipients chosen to manufacture the powder can be altered to provide desired effects such as controlled release of the drug. Once processed, the powder can be directly packaged into sachets, compressed into tablets or filled into capsules. Tablets can further be coated in order to improve palatability or provide controlled release of the drug.

Oral liquid dosage forms are primarily used by the pediatric population and those who experience difficulty in swallowing. Liquid dosage forms are available as solutions, suspensions or emulsions. These liquids often contain colorants and flavorings in an attempt to increase palatability and patient acceptance.

Many patients, however, are unable to adequately ingest either solid or liquid dosage forms. To address this problem, health care providers often crush solid dosage forms and disperse them in a semi-solid medium (e.g., applesauce, pudding). However, when tablets or capsules are tampered with the drug release kinetics of the pharmaceutics are altered. This can result in dose dumping, i.e., serum concentrations which are non-optimal, and can be dangerous.

There are a number of drug administration and patient compliance issues peculiar to the geriatric market, which result from hard to swallow tablets, unpleasant taste and texture, frequent

dosing regimens or unfavorable side effect profiles of certain drugs. Current tablet and liquid dosage forms do not address the needs of the elderly patient. Physical limitations prevalent amongst the elderly hinder their ability to swallow traditional dosage forms and to self-administer medication (e.g., arthritis, tremors associated with neurological disorders, visual impairment, and memory problems). Physical limitations present in this age group include difficulty in swallowing due to dehydration, "mouth breathing", and esophageal lesions. Chewing also is difficult due to reduced bulk and tone of oral musculature as well as loss of, or degradation, in the quality of their teeth.

Other patient populations present drug administration and patient compliance issues. These include pediatric patients (2-6 years old), certain oncology patients, late-stage AIDS patients, post-surgical patients and patients who have other advanced disease states which are physically debilitating.

There remains a need for dosage formats that are compatible with such populations and that address the physical and physiological limitations of these populations. There remains a need to provide dosage formats that can be administered to patients who experience difficulty in swallowing solids (i.e. tablets or capsules) and liquids.

In attempts to solve some of the above issues, different formulations of nano- or micro-granules have been reported (see, US 5,618,527). These formulations consist of spherically-shaped particles in either a liquid or a tablet form, in which the particles are not greater than 125 μm in diameter to avoid the sensation of grittiness. Also, the particles need to have smooth edges. These requirements severely limit the flexibility of the drug manufacture and delivery.

A similar attempt to reduce the sensation of grittiness was described by using a blend of a gritty drug with a seedy fibrous fruit (US 5,102,664). In this combination the seedy fibrous fruit texture masks the grittiness of the drug. The problem of grittiness also is evidenced in certain topical formulations. Topical formulations which contain particles of drugs (or particles containing drugs) have an unpleasant gritty feel when applied to the skin.

There exists the need for a drug delivery format which is adaptable to patient populations that have trouble chewing and swallowing. There also exists a need for a drug delivery system which is adaptable to all formats, including oral, topical, injectable, and other delivery formats. There also is a need for a drug delivery system that can permit adjustment of the release profile of the drug. Various aspects of the present invention address the foregoing needs.

Summary of the Invention

The present invention provides novel methods and products for the manufacture and use of novel drug delivery systems. The invention involves the discovery that very small flakes have a better mouth feel than microparticles and can be used to deliver drugs, vitamins, minerals, essential nutrients and herbal bioactive agents, preferably orally, to various subjects, including especially geriatric individuals, children, and certain medically impaired individuals.

According to one aspect of the invention, a composition is provided. The composition is a plurality of discrete, substantially flat flakes, each having an average length, an average width and an average thickness, wherein each of the length and the width are at least three times the thickness, wherein a longest dimension of each flake is between 100 nanometers and 5 millimeters, and wherein the flakes comprise a drug, a nondrug active agent or a nonnutritional active agent. The flakes can comprise an agent selected from the group consisting of:

(a) an effective amount of a drug, and

(b) an effective amount of a nondrug active agent, provided that if the agent is only a nondrug active agent, then the nondrug active agent is selected from the group consisting of

(i) at least 1.0% by weight of the flakes of a noncalcium nondrug active agent selected from the group consisting of a vitamin and a mineral,

(ii) at least 3.0% by weight of the flakes of a nondrug active agent selected from the group consisting of a vitamin and a mineral, and

(iii) at least 3.0% by weight of the flakes of a nondrug active agent that is an essential nutrient,

(iv) at least 1.0% by weight of the flakes of an herbal bioactive agent combined with a binder and formed into the flakes, and

(v) a coated herb.

In one embodiment, each of the flakes has a surface area, and the ratio of the surface area to the thickness is at least 25 units ^{2}:1 unit. In another embodiment, the longest dimension of each flake is between 10 microns and 1 millimeter. In still another embodiment, the ratio of the surface area to the thickness is at least 100 units ^{2}:1 unit. Preferably, the flakes are less than 200 microns, less than 150 microns, or less than 125 microns in thickness. Even more preferable are flakes less than 75 microns or even less than 60 microns in thickness.

The agent can comprise a very small amount of the flakes or it can comprise a very large amount of the flakes by weight. Thus, the agent can comprise between 0.001% and 100% by

weight of the flakes. In certain embodiments, the agent is at least 0.05% of the flakes by weight. In other embodiments, the agent is at least 2%, at least 3%, at least 4% or at least 5% of the flakes by weight. In still other embodiments, the agent is at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 12.5%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, or at least 50% of the flakes by weight.

The agent can be embedded within the flakes or the agent can be coated on the flakes. If the agent is embedded within the flakes, then the flakes can be made entirely of the agent or the agent can be dispersed throughout all or a portion of the flakes. If the agent is dispersed throughout the flake, then the agent can be a component of the flake, can be contained in discrete pores within the flake, can be contained in discreet microparticles dispersed through the flake, can be in one or more layers comprising the flake, can be physically and/or chemically retained within a flake which comprises a porous matrix etc. The agent also can be coated on a surface of the flakes. The coating can be an even continuous coating or can be a noncontinuous coating. The agent can be contained in microspheres which are coated on the flakes. The agent also can be coated directly onto the flakes or can be attached covalently or noncovalently to the flakes by linking agents.

In one important embodiment, the flakes thus further comprise a coating on the flakes. This coating can, in some embodiments, separate the agent from the environment. The coating can be an enteric coating covering the flake. The coating also can be an extended-release coating, a taste masking coating, a pH sensitive coating, a temperature sensitive coating, a bioadhesive coating, or a color coating. Other coatings are described below.

The flakes can be made of any one of a variety of materials, polymers or non-polymers, discussed in greater detail below. The flakes can comprise natural or synthetic polymers. In some embodiments, the flakes are at least 10%, at least 15%, at least 20% or at least 25% by weight of the polymer. In many embodiments, the flake is at least 5%, at least 10%, at least 20%, at least 25% a nonfood by weight. In most embodiments, the flake is at least 25%, at least 50% and at least 75% of a nonfood by weight.

The flakes also can comprise a drug enhancing agent. A drug enhancing agent is an agent which potentiates the activity of a drug, enhances the uptake of a drug, helps with the side effects caused by the drug, etc. An example of a drug potentiating agent is an agent which inhibits degradation of the drug, thereby extending its activity. In other embodiments, the flake can comprise a drug uptake enhancer. A drug uptake enhancer is a material which, when it is

administered together with the drug, facilitates uptake of the drug in the environment in which the drug is delivered. Agents which potentiate the activity of a drug, help with the uptake of a drug, or favorably affect a side effect associate with the drug are well known for a variety of drugs and are approved by the FDA. The drug enhancing agent also can be present in a pharmaceutically acceptable carrier for the flakes, such as a fortified carrier or nutritionally fortified carrier as discussed in greater detail below.

The flakes also can comprise at least 2, at least 3, at least 4 or more layers. Each of the layers can be the same or a different composition. Each of the layers may or may not contain an active agent. The invention also contemplates the plurality of flakes being a mixture of two different types of flakes, a first type carrying a first agent and a second type carrying a second agent.

In certain embodiments, the flakes are packaged in unit doses, such as in small cellophane or foil compartments, sachets or capsules. In one preferred embodiment, the flakes are in a capsule which is provided with grips, whereby, for example, a person may easily grip the sides of the capsule to pull the two halves of the capsule apart. In this manner, the contents of the package can be mixed with a physiologically acceptable carrier, including food, a semi-solid nonfood carrier or a liquid. In another embodiment the flakes are formed with an excipient into a tablet. The tablet can be a taste-masked, fast-dispensable tablet containing excipients for immediate dispersion when introduced into the mouth. Such tablets are known in the art, but have never before been loaded with flakes. The tablet also can be a chewable tablet, wherein the excipients promote salivation and/or swallowing (e.g. sugars and lubricants), whereby chewing releases the excipients and the flakes.

In certain preferred embodiments, the agent is a drug and the drug is selected from the group consisting of: furosemide, digoxin; potassium chloride; divalproex; trazodone-HCl, ranitidine; phenytoin sodium, sertraline-HCl, risperidone, omeprazole; folic acid; haloperidol; nizatidine; carbamazepine; metoprotol tartrate; lisinopril; warfarin; cisapride; hydrochlorothiazide; nitroglycerin; methyldopa; carbi-dopa/levodopa; prazosin; oral hypoglyceremics; amantadine-HCl; hyoscyamine sulfate; fluoxetine; nifidipine; diltiazeim; phenotoxifyline; ketoprofen; aspirin; piroxicam; indomethacin; ibuprofen; isotretinoin; triamtevene.

In other preferred embodiments, the agent is a drug and the drug is selected from the group consisting of: isotretinoin, oxazepain, lorazepam, piroxicam, loperamide,

bromopheniramine, phenylpropanolanime, loratadine, famotidine, ordansetron, enalapril, captopril, phloroglucinol, nicergoline, acetaminophen, metapimazine, dihydroergotamine, fexofenadine-HCl and albuterol.

In certain embodiments, the agent is a plurality of drugs, and the plurality of drugs is selected from the group consisting of: (a) furosemide and potassium chloride, (b) metolazone and potassium chloride, (c) Levadopa and carbadopa, (d) Levadopa/carbodopa and docusate sodium/bisacodyl, (e) tylenol/codeine and docusate sodium/disacodyl, (f) tricyclic depressants and docusate sodium/bisacodyl, (g) warfarin and nizatidine, (h) amoxicillin and clavulanate, and (i) imipenem and cilastatin.

In other embodiments, the agent is selected from the group consisting of: (a) Vitamin D and calcium, (b)Vitamin D, calcium and magnesium, (c) at least 10 vitamins and minerals, and (d) Vitamin C, Vitamin E and Vitamin A.

It will be understood that the invention also includes embodiments which are obvious combinations of the foregoing embodiments and limitations. For example, a coating can be applied to any of the foregoing flakes, without regard to the weight percent of the agent in the flake, without regard to whether the flake is a multiple layered flake and without regard to whether the flakes comprise a mixture of flakes or a mixture of drugs and/or vitamins and/or minerals and/or herbal agents.

According to another aspect of the invention, another composition is provided. The composition is a plurality of discrete, substantially flat flakes, each having an average length, an average width and an average thickness, wherein each of the length and the width are at least three times the thickness, wherein the longest dimension of each flake is between 100 nanometers and 5 millimeters, and wherein each flake comprises a nonfood porous matrix. The pores are large enough to accommodate a drug or a nondrug active agent. In this aspect of the invention, the composition can further comprise a drug or nondrug active agent. The flake in some embodiments is at least 5%, at least 10%, at least 25%, or at least 50% a nonfood. Important embodiments such as dimensions, ratios, type of agent, percent agent by weight contained within the flake, and so on are as described above.

According to another aspect of the invention, a composition is provided. The composition is a plurality of discrete, substantially flat flakes, each having an average length, an average width and an average thickness, wherein each of the length and width are at least three times the thickness, wherein the longest dimension of each flake is between 100 nanometers and

5 millimeters. and wherein each flake comprises a nonfood porous matrix, and a vitamin, wherein the flakes are at least 20%, at least 50%, or at least 75% by weight nonfood. In some embodiments, the vitamin is present in an amount of at least 0.5% by weight of the flake, at least 1% by weight of the flake, at least 2% by weight of the flake, at least 3% by weight of the flake, at least 4% by weight of the flake, at least 5% by weight of the flake, at least 10% by weight of the flake, at least 15% by weight of the flake, at least 20% by weight of the flake or at least 25% by weight of the flake. Important embodiments such as preferred dimensions, ratios, type of vitamin, and so-on, are as described above.

According to another aspect of the invention, a pharmaceutical preparation is provided. The pharmaceutical preparation contains any one of the compositions as described above, and, optimally, a pharmaceutically acceptable carrier. In this embodiment the flakes themselves are pharmaceutically acceptable agents and excipients. The pharmaceutical composition can contain an amount of a drug effective for treating a condition treatable by the drug. In certain embodiments, the pharmaceutical preparation is formulated as an oral dosage form. The oral dosage form can be in a container such as a capsule containing the drug containing flakes which can be opened and sprinkled over or into a pharmaceutically acceptable carrier. In another embodiment, the pharmaceutical preparation is formulated as a topical preparation. The topical preparation can contain an agent that is non-suitable for oral ingestion. In still another embodiment, the pharmaceutical preparation is formulated as an implant. In yet another embodiment, the pharmaceutically acceptable carrier is a semi-solid. The semi-solid can be a hydrogel or a food. A semi-solid, viscous liquid or liquid carrier also can be fortified with a drug enhancing agent and/or a nutritional fortification agent. The flakes can be coated as described above. These flakes can be controlled-release forms, e.g.: delayed-release forms, timed-release forms, targeted-release forms, sustained-release forms and the like. They also can be coated with a taste-masking composition.

According to still another aspect of the invention, a method is provided for treating a subject having a condition. The method involves administering to a subject in need of such treatment an amount of a drug effective to treat the condition, wherein the drug comprises a plurality of flakes. In important embodiments, the flakes comprise any one of the pharmaceutical preparations as described above. In another important embodiment, the drug is administered orally. In another important embodiment, the subject has a condition making it difficult to swallow. The subject preferably can be selected from the group consisting of a

geriatric subject, a subject with cancer, a subject who is post-surgically recovering, an infant, a child, or a late-stage AIDS subject. Conditions embraced by the claims re detailed below.

According to yet another aspect of the invention, a method is provided for preparing a pharmaceutical preparation. The method is an improvement to the known methods for forming pharmaceutical preparations by incorporating a drug within or coating a drug onto a particle, the improvement comprising incorporating the drug within or onto a flake. In important embodiments, the flakes are as described above.

The invention thus involves methods for preparing flakes which incorporate drugs, vitamins, minerals, essential nutrients and herbal active agents. The flakes may be made in any variety of methods, including printing by ink jet, spraying onto a web or drum for drying, spraying onto a membrane, extruding, cutting and drying, stamped, rolled and stamped, crystallized into flakes, crystallized onto sheets, drums, etc. in any one or more of the foregoing methodologies, the flakes may additionally be layered such as by spraying onto a substrate more than one layer of material or by placing a pair of sheets in contact with one another and stamping the sheets. In important embodiments, the flakes are manufactured by coating them with controlled-release coatings, as described in greater detail below. In addition, they can be coated with flow agents to keep the flakes flowing in dry form and anti-static agents to avoid the flakes sticking to one another. They also can be coated with detergents/surfactants to break the surface tension to allow flakes to be wetted faster. Particularly important coatings are polymer coatings and hydrogel coatings.

According to another aspect of the invention, a method is provided for preparing a pharmaceutical preparation. The method involves incorporating a drug into or upon a plurality of flakes. In one embodiment, the flakes are formed first, and then the drug is coated onto, or allowed to penetrate into, the flakes. In another embodiment, the drug is incorporated into the flakes by forming the flakes in the environment of the drug. In another embodiment, the flakes are coated with any of the coating agents described above.

The invention has been described in this summary in connection with agents including drugs. Drugs include therapeutic and diagnostic agents. Drugs are defined herein as excluding nutritional supplements. Thus, drugs are not nutritional supplements such as vitamins and minerals. The agent carried by the flakes of the invention, however, need not be a drug. The agent can be a nondrug active agent such as a vitamin, a mineral, an essential nutrient or can be

an herbal active agent. The agent also can be a nondrug active agent such as an insect repellant, a sunscreen agent, a pesticide, etc. Classes of nondrug agents are described below.

The invention also contemplates both food and nonfood flakes. In some embodiments of the invention the flake is a nonfood such as a synthetic polymer for carrying the drug or other active agent. It is an embodiment of the invention, however, that the flake can be a food such as an oat flake or a grape nut flake. The flake also can be a natural wheat bran flake, a processed rice flake or a formed pea pod flake. When the flake is a food, then the drug either is not a nutritional supplement, or, if it is a nutritional supplement, it is present at levels totally uncharacteristic of the levels of the prior art. For example, fortified rice flakes are known in the prior art as an infant's cereal. The flakes are fortified with minor amounts of vitamins and minerals, such as on the order of 1.2% by weight of the flake in total (for example, for 15 different vitamins and minerals). The present invention, on the other hand, involves the manufacture of flakes carrying a much greater percentage of vitamins and minerals, such as would be characteristic of a vitamin tablet. A small amount of the flakes of the present invention, therefore, can be substituted for vitamin tablets which are difficult to swallow for certain patient populations. Thus, the invention intends to exclude the prior art nutritionally supplemented food flakes such as fortified oatflakes and fortified cereal flakes.

It is known that a variety of drugs have enhanced therapeutic effects due to improvements in drug delivery when delivered together with a drug enhancer. Such enhancers can be included with a drug in a single flake or can be provided separate from the drug carried on its own flake. Thus, the plurality of flakes can be mixtures of flakes, some containing a drug and some carrying nondrug component, that act as an adjunct to therapy. One important example of this is flakes which have anti-constipation properties. Many drugs cause constipation and many patients such as geriatrics are chronically constipated. Flakes which are a mixture of drugs and anti-constipation agents are useful for such patient populations.

According to another aspect of the invention, an article of manufacture is provided. The article is a capsule defining a chamber and a plurality of discrete, substantially flat flakes, each having an average length, an average width and an average thickness, wherein each of the length and width are at least three times the thickness, wherein a longest dimension of each flake is between 100 nanometers and 5 millimeters, wherein the flakes are contained within the chamber of the capsule. In one embodiment, the flakes comprise a drug. In another embodiment, the capsule is a pair of closed-end mating cylinders, each of the pair provided with a non-smooth

gripping surface. The gripping surface may be, for example, etchings, grooves, protrusions, ridges, and the like.

According to another aspect of the invention, a tablet is provided. The tablet contains flakes as described for the capsule. The flakes can comprise a drug and can be coated or uncoated, more than one layer, etc. The tablet can also be coated or uncoated. The tablet can be, for example, chewable or fast-dispensable (including excipients to promote the same).

The present invention also provides a spoon-feedable drug delivery vehicle. The vehicle includes a viscose base having a consistency capable of being spoon-fed. The viscous base may be food or non-food. Particles comprising a drug and, optionally, a synthetic or natural carrier are added to or mixed into the viscose base. The particles may have any suitable size and shape, such as by way of example, spherical, oblong, and flake-like particles as described above. The drug may be provided premixed with the base, or it may be supplied separately from the base for mixing just prior to consumption. In the latter case, hits are provided, which contain both the drug and the delivery vehicle, separately packaged.

The spoon-feedable drug delivery vehicle also can be a nutritionally fortified delivery vehicle. It can have a semi-viscous or semi-solid consistency which may be readily spoon-fed. This base may be supplied in a unit dose package in a variety of flavors and compositions. It provides a spoon-fed base for administration of drugs which addresses the difficulties in some patient populations intolerant of orally delivered medication. In addition, it can provide necessary dietary nutrients and/or fiber.

Brief Description of the Drawings

Fig. 1 is a flake-making rotary-drum apparatus according to the invention.

Fig. 2 is a capsule according to the invention.

Detailed Description of the Invention

It has been observed that spherical or granular particulates leave a gritty sensation in the mouth which can be unpleasant to the patient when administering micro-granules. In addition, in order to administer medications to geriatric patients who have difficulty swallowing tablets, nurses frequently crush the tablet into gritty particles and mix the particles with food, destroying the coating on the tablet and potentially altering the release profile/availability of the drug. The present invention has recognized that drugs which are incorporated into a flaked delivery vehicle

possess enhanced mouth feel by eliminating or reducing the gritty feel characteristic of the prior art particles. The flakes of the present invention will be better tolerated by the patient, leading to more complete dosages and higher compliance when used for oral delivery.

A flake is a substantially flat, thin layer or unit and thus possesses a dimension which is substantially less than the other two dimensions. The flake may be substantially planar or similar to curvilinear. The flake may be solid or porous. It may be virtually any shape about the perimeter of the planar surface, such as round, oval amorphous about its perimeter, oblong, etc. It may be crystalline, even as in a snowflake.

In a preferred embodiment, the flakes are substantially flat, each having an average length, an average width and an average thickness, wherein each of the length and width are at least three times, and preferably at least five times the thickness, and wherein the longest dimension of each flake is between 100 nanometers and 5 millimeters. If, because of the shape of the flake, an "average" length and width cannot be readily determined, then the longest length can be substituted for the "average length" and longest width measured transversed to the longest length can be substituted for the "average width" in making this determination. It is important only that the flake be wafer-like, that is, thin in one dimension and substantially flat (as distinguished from spherical, spheroidal or amorphous. Preferably, the flakes are 125 microns in thickness, or less. Particles are said to lose their grittiness at 60 microns. Flakes lose their gritty feel at above this thickness, although flakes 60 microns in thickness or less also can be made according to the invention. Preferably, the flake has a size of between 10 and 500 microns along its longest dimension. The flakes preferably are free flowing. The flakes can be relatively uniform and consistent in size and morphology or can be a mixture of flakes of different sizes and morphologies.

The invention involves in one aspect the delivery of agents in or on such flakes. A "plurality" of flakes is referred to. A plurality means greater than 100. In important embodiments, the plurality is greater than a thousand, greater than ten thousand and even greater than one hundred thousand.

The flakes can be non-porous or porous. The flakes can be made entirely of the agent or can be as low as 0.001% agent-containing. Thus, the agent may be combined with any of the variety of normal excipients, binders, fillers and the like and formed into a solid flake. The excipients may be non-polymers or polymers. In one important non-polymer embodiment, which is merely exemplary, the flake is a "fused" flake. In a "fused" flake, a drug, a carrier, or

both are melted and recrystallized to form a crystalline matrix of the drug and/or carrier. In a totally fused flake, both the drug and the carrier are melted and recrystallized. In a partially fused flake, only the carrier is melted and recrystallized, thereby capturing the drug in the crystalline matrix of the carrier. Sterols are particularly suited for melting and recrystalization. For example, various cholesterol-type compounds, including cholesterol acetate may be used. Compounds such as palmitic acid also can be used. Detailed parameters about forming "fused" drug delivery materials are disclosed in U.S. patent numbers 4,748,024, 4,892,734 and 5,039,660, the entire disclosures of which are incorporated herein by reference. These patents illustrate that virtually any amount of drug and carrier, including no carrier, can be used in the formation of such materials.

The excipient also may be a polymer. The types of polymers that may be used are described in great detail below. The polymers are substantially coextensive with the materials which are used in connection with making nano- and microparticles or spheres (hereinafter "microparticles"). Such polymers further include bioadhesives which are particularly suited for oral delivery methodologies, as is described and known in the prior art. Using such polymers, nonporous flakes can be manufactured or porous flakes can be manufactured. The agent can be loaded into the flake during the manufacture of the flake or may be added to the flake after the manufacture of the flake, by causing the agent to be absorbed into or adsorbed onto the flake or by coating the agent onto the outside surface of the flake. In the various methodologies used for manufacturing microparticles, it is shown that an agent can be physically entrapped within the polymer, chemically bound within the polymer (covalently or noncovalently) or physiochemically entrapped within or bound to the polymer. The present invention does not involve the use of new polymers and the like, but instead involves the use of known technology for drug delivery with the exception that the materials are manufactured and fashioned in the form of a flake rather than in an amorphous or spherical particle.

The substantial majority of the flake, thus, can be a nonfood such as a natural or synthetic polymer. Flakes made from foods also may be used according to the invention. Originally, any food material could be combined with binders, excipients, and the like in order to form flakes for carrying agents according to the invention. Preferred materials are those presently used in the formation of flakes, such as rice flakes (for baby cereal) and ground pea pods. Additionally, some foods exist in the form of flakes, such as wheat bran which is a naturally occurring flake.

In the same manner as discussed above in connection with polymers, the agent can be loaded into the flake during manufacture or can be added to the flake after manufacture.

The release dynamic of drugs from the flakes can be controlled in a conventional manner, just as the release profile of drugs is controlled in other similar technologies such as in a particle-based or polymer-based delivery systems. According to the invention, therefore, flakes can be manufactured so as to control and/or vary parameters such as size, morphology, materials and coatings to influence release of drugs from the flakes. Controlling such parameters can achieve drug release profiles as desired, including delayed-release, timed-release, targeted-release, and sustained-release. One advantage of the flakes according to the invention is that the release profile can be made more uniform, because, unlike for a particle or sphere, the surface area of a flake is relatively constant as it erodes. In any event, virtually any release profile can be achieved using technologies which are well known to those of ordinary skill in this art.

A principal characteristic of size which affects the length of time over which agents are released is the thickness of the flake. The thicker the flake, of course, the longer the period of time over which the agents will be released, all other parameters being kept equal. This is particularly so if the flake is bioerodable. The flakes also can be of different surface areas, which will affect the release kinetics of agents contained therein or coated thereon. The plurality of flakes, therefore, can be a mixture of sizes, uniformly distributed over a range or be two or more discrete sizes to achieve a pulsed-type release, etc. The flakes can be relatively large so as to lend themselves to topical and oral delivery formats or can be extremely small, permitting them to be injected.

The morphology of the surface of the flakes also will affect the release profile of agents from the flake. Smooth surfaces represent relatively smaller surface areas, whereas rough surfaces represent relatively larger surface areas, as is well known.

The materials from which the flakes are made also will affect the release profiles of agents from the flakes. Again, this is well known to those of ordinary skill in this art. For example, a flake formed of melted and recrystallized drug and/or carrier will dissolve more slowly than a drug and/or carrier that simply are pressed into a flake without melting, due to the energy of the crystal lattice of the melted and recrystallized material. At one extreme, the flake can be made of a polymer or fiber that is not bioerodable, whereby the only drug released is that which diffuses from or is released by the flake as it passes through the gastrointestinal tract. At another extreme, the flake can be made of a material that erodes completely when applied

topically or systemically, such as before it passes through the gastrointestinal tract. Such flakes can be made of materials which erode selectively in the stomach, materials which erode selectively in the small intestine, materials which erode selectively in the large intestine, or materials which will erode partially or completely in more than one of these selected tissue regions.

The flakes also can be made of ion exchange materials to cause a selective release of agents in a particular tissue. One example is using a resin that will release a drug in the presence of high concentrations of sodium ions, such as are present in the small intestine. The flakes also can be manufactured from a mixture of monomers and agent, whereby the monomer is polymerized into a polymer about the agent to form a 'molecularly imprinted polymer', which acts as a cage for the agent molecule. Thus, the flakes may be made of biodegradable polymers and non-biodegradable polymers and non-polymers as is conventional, all selected to influence the release profile of the agent.

One important class of polymers useful in the invention are the bioadhesive polymers. Such polymers can be fashioned as flakes containing drugs and will adhere to the intestine. This can accomplish a number of desirable results. First, it can increase residence time of the flakes in the intestine, thereby affecting the amount of drug released in the intestine. In addition, the bioadhesive-containing drug will stick to the intestine, and act as a sustained-release delivery form for such time as it is present sticking to the intestine. The drug will be released slowly by diffusion or through degradation of the polymer in the intestine, thereby controlling the release profile of the drug.

The flakes also can be coated, applying principals conventional in the particle-based delivery art. Thus, the flakes can be coated with enteric coatings to permit the flakes to survive the environment of the stomach. The flakes can be coated with pH-sensitive materials to cause the coating to dissolve only after the flake enters the intestine. Coatings which would dissolve at neutral pH, generally, are useful for this purpose. The flakes also can be coated with lipophilic coatings which tend to dissolve only after contacting the bile in the large intestine. Such coatings also can be taste-masking coatings, such as is described in U.S. patent 5,084,278 and the patents cited therein, the disclosure of which is incorporated herein by reference. The present invention does not present new coating technology, but instead the flake particles of the present invention can be coated in the same manner as the prior art particle and microparticle delivery technologies. The coatings may be made from the same material as the flake or from different

materials. The coatings can be adapted to protect the agents contained in the flakes. to provide advantages to the flakes in their environment of use (such as by permitting the flake to pass through the stomach), to cause the flakes to be less likely to aggregate with one another (making them flowable such as by coating with an antistatic agent), to provide a layer of a second drug, to provide a layer of a drug at a different concentration, to provide color, to provide controlled release (including targeted release) and the like.

The thickness of such coatings, of course, also can be varied, whereby some flakes are exposed for agent delivery prior to others, thereby effecting an extended agent-release profile.

The coatings may be free of agent or may contain the agent. If the coating contains an agent and the flake also contained an agent, then it can be the same agent or a different agent than is in the flake. If it is the same drug, it can be of the same concentration or at a different concentration. Likewise, the coating can be made of the same material as the flake or of a different material than the flake. Thus, the flake can be a particular polymer containing a drug, and the coating can be the same polymer free of drug or the coating can be a different material altogether. It should be mentioned, as well, that the flake can contain a single agent or a combination of agents.

The flakes also can be formed of a variety of layers, some of which can act as a coating. One layer can be a drug and another layer can be, inter alia, (1) a coating to influence the drug-release profile, (2) the same drug but at a different concentration, (3) a different drug, (4) a barrier layer to separate two layers, (5) a substrate for another layer, (6) a food, (7) a nonfood and so on. Thus, the flakes according to the invention may be 1, 2, 3, or more layers. Such layered flakes can be manufactured easily, such as, for example, by pressing two or more layers together, by spraying a plurality of layers sequentially onto a belt or drum, by vortexing or otherwise suspending preformed flakes to render them airborne in a mist that will coat the flakes to create another layer, and so on.

Flakes having any one or more of the foregoing characteristics can be manufactured by adapting existing technologies to flake manufacturing processes. For example, agents can be incorporated into flakes at different concentrations by applying two agents to two separate preparations of prefabricated porous flakes, the agents at different concentrations in solutions for diffusing into the two separate preparations of flakes. Coatings of various thicknesses also can be applied as is conventional. Single, double, triple, and other multi-layered flakes, coated or not, thus can be formed. Mixtures of flakes with different characteristics also can be used, e.g. uncoated flakes with coated flakes, mixtures of flakes with different concentrations of drugs, mixtures of

flakes with different thicknesses, mixtures of flakes carrying drugs with flakes that carry drug uptake enhancers, etc.

According to one important embodiment, the sustained or controlled release microparticles of the prior art are used conventionally in the flake technology of the present invention. In this aspect of the invention, microparticles, such as microspheres and nanospheres, are incorporated into the flakes of the invention. In other words, microparticles first are formed having known and desired release-profiles characteristic of the prior art. Those microparticles then are formed as part of the flakes of the invention. The microparticles can be pressed into flakes, sprayed onto rotating drums as described in greater detail below and formed into flakes, covalently attached to flakes and the like. Thus, in order to achieve the release profiles characteristic of the prior art, no new technology is required. Instead, the flakes simply can act as a delivery vehicle for existing microparticles. Such a delivery vehicle would be particularly useful for oral preparations, topical preparations, and in other circumstances as will be apparent to those of ordinary skill in the art.

It has been mentioned that one important use of the flakes of the invention is for delivering agents orally. Any agent which can be delivered orally according to the prior art microparticle technology can be delivered using the flake technology of the invention. Virtually any release profile obtained in the prior art using oral delivery formats also can be obtained using the flakes according to the invention. The flakes simply provide a convenient format for orally delivering drugs to particular target patient populations.

The flakes also can be used in topical formulations. The flakes will provide a smooth, non-gritty coating on the skin, which can be used for delivering topically agents contained in or attached to the flakes. Such topical preparations include virtually all of the known agents presently delivered topically, but never before delivered as part of a flake. In addition, the flakes are particularly suited for the delivery of certain agents, such as sunscreen agents and insecticides. For sunscreen agents, the flakes themselves could comprise a physical or chemical sunscreen agent, which could be used to form a protective barrier from the sun. Moreover, if the sunscreen agent is covalently attached to the flake, then the sunscreen agent can be prevented from entering cells, thereby reducing or even eliminating any side effects for such sunscreen agents. The agent is held on the flake and is not released into the skin. The same benefit can be obtained when using flakes according to the invention to apply an insecticide. The insecticide can be covalently attached to the flakes which are topically applied as a smooth layer on the skin. Because the insecticides are covalently attached to the flakes, they are present for exerting the desired action, but they are not

released generally in high dose into the skin, thereby avoiding potentially unwanted side effects. Such sunscreen agents and insecticides on flakes also are desirable as the flakes themselves act as a smooth lubricant when applying the agents to the skin.

In topical preparations, the flakes, in general, are lubricating and therefore can prevent chafing of skin against skin or clothing against skin, as an additional benefit.

Flakes according to the invention also may be applied in preparations that are intended for body cavities, such as intravaginal preparations or suppository preparations. Agents such as antibiotics, antifungals, and the like can be attached to flakes and conveniently delivered. The feel of such flakes is superior to the feel of the microparticles of the prior art.

Such topical preparations can include agents for treating genital warts, kaposi sarcoma, actinic keratosis and skin cancers in general.

The topical preparations of the invention also can be used for applying wound healing agents to the skin. The wound healing agents can be attached to, coated on, or contained within the flakes of the invention, which can be applied topically.

The flakes according to the invention also can be applied parenterally. The preparations of the invention are particularly suitable for local delivery of drug agents. The flakes of the invention have less mobility than microspheres when placed within the body, such as by injection into a solid tumor. Systemic exposure to the drug thereby is reduced and it is believed that a more consistent release profile is obtained. The flakes of the invention also can be used in a manner as described in the prior art by intravenous injection, whereby the flakes are manufactured at a particular size and become desirably lodged in capillaries.

Flakes according to the invention also can be used to cover areas in the body to prevent tissue adhesion, such as post-surgical tissue adhesion. The flakes can be made, for example, of hyaluronic acid, and applied to cover areas of tissue to prevent tissue adhesions.

The flakes of the invention thus can be included in any of the prior art forms used for administering drugs, including implants, topical preparations, inhalable preparations, suppositories, ocular formulations, oral formulations and the like, which are well known. In certain of the preparations according to the invention, such as topical preparations, there may be included agents which are not suitable for oral ingestion. Such agents include creams, lubricants and the like which are well known.

Exemplary polymer materials for making flakes include polyvinyl alcohol, poly(vinylpyrolidone), methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose,

agar, carrageenan, xanthan, polyethylene glycol, a copolymer of acrylic and methacrylic acid esters, ethylcellulose, cellulose acetate, cellulose acetate phthalate, poly(methyl methacrylate), poly(methyl acrylate), polyethylene, polypropylene, polyethylene oxide, poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethane, pectin, furcellaran, starch, zein, gelatin, collagen, polygeline, alginic acid, propylene glycol alginate, sodium carboxymethylcellulose, lactose, sucrose, dicalcium phosphate, or sodium alginate.

A more comprehensive list is materials including, but not limited to, nonbioerodable and bioerodable polymers. Such polymers have been described in great detail in the prior art. They include, but are not limited to: polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terepthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and copolymers thereof, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly (methyl methacrylate), poly(ethylmethacrylate), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexlmethacrylate), poly(isodecylmethacrylate), poly(lauryl methacrylate), poly (phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylene, polypropylene poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohols), poly(vinyl acetate, poly vinyl chloride polystyrene and polyvinylpryrrolidone.

Examples of preferred non-biodegradable polymers include ethylene vinyl acetate, poly(meth) acrylic acid, polyamides, copolymers and mixtures thereof.

Examples of preferred biodegradable polymers include synthetic polymers such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyurethanes, poly(butyric acid), poly(valeric acid), poly(caprolactone), poly(hydroxybutyrate), poly(lactide-co-glycolide) and poly(lactide-co-caprolactone), and natural polymers such as alginate and other polysaccharides that include but are not limited to arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans (such as, for example, inulin), levan, fucoidan, carrageenan, galatocarolose, pectic acid, pectin, amylose, pullulan, glycogen, amylopectin, cellulose, dextran, pustulan, chitin, agarose, keratan, chondroitan, dermatan, hyaluronic acid, alginic acid, xanthan gum, starch and various other

natural homopolymer or heteropolymers such as those containing one or more of the following aldoses, ketoses, acids or amines: erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, mannitol, sorbitol, lactose, sucrose, trehalose, maltose, cellobiose, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, glucosamine, galactosamine, and neuraminic acid, and naturally occurring derivatives thereof, and including dextran and cellulose, collagen, chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo*, by surface or bulk erosion. The foregoing materials may be used alone, as physical mixtures (blends), or as co-polymers. The most preferred polymers are polyesters, polyanhydrides, polystyrenes and blends thereof.

Particularly preferred in some embodiments are bioadhesive polymers. A bioadhesive polymer is one that binds to mucosal epithelium under normal physiological conditions. Bioadhesion in the gastrointestinal tract proceeds in two stages: (1) viscoelastic deformation at the point of contact of the synthetic material into the mucus substrate, and (2) formation of bonds between the adhesive synthetic material and the mucus or the epithelial cells. In general, adhesion of polymers to tissues may be achieved by (i) physical or mechanical bonds, (ii) primary or covalent chemical bonds, and/or (iii) secondary chemical bonds (i.e., ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bioadhesive properties, consist of dispersive interactions (i.e., van der Waals interactions) and stronger specific interactions, which include hydrogen bonds. The hydrophilic functional groups primarily responsible for forming hydrogen bonds are the hydroxyl and the carboxylic groups. Numerous bioadhesive polymers are discussed in that application. Representative bioadhesive polymers of particular interest include bioerodible hydrogels described by H.S. Sawhney, C.P. Pathak and J.A. Hubell in Macromolecules, 1993, 26:581-587, the teachings of which are incorporated herein, polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly butylmethacrylate), poly(isobutylmethacrylate), poly(hexlmethacrylate), poly(isodecl methacrylate), poly(lauryl methacrylate), poly(phenyl

methacrylate), poly (methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecl acrylate). Most preferred is poly(fumaric-co-sebacic)acid. Other suitable bioadhesives are pectin, a mixture of sulfated sucrose and aluminum hydroxide, hydrophilic polysaccharide gums such as natural plant exudates, including karaya gum, ghatti gum, tragacanth gum, xanthan gum, jaraya gum and the like, as well as seed gums such as guar gum, locust bean gum, psillium seed gum and the like.

Polymers with enhanced bioadhesive properties can be provided wherein anhydride monomers or oligomers are incorporated into the polymer. The oligomer excipients can be blended or incorporated into a wide range of hydrophilic and hydrophobic polymers including proteins, polysaccharides and synthetic biocompatible polymers. Anhydride oligomers may be combined with metal oxide particles to improve bioadhesion even more than with the organic additives alone. Organic dyes because of their electronic charge and hydrophobicity/ hydrophilicity can either increase or decrease the bioadhesive properties of polymers when incorporated into the polymers. The incorporation of oligomer compounds into a wide range of different polymers which are not normally bioadhesive dramatically increases their adherence to tissue surfaces such as mucosal membranes.

As used herein, the term "anhydride oligomer" refers to a diacid or polydiacids linked by anhydride bonds, and having carboxy end groups linked to a monoacid such as acetic acid by anhydride bonds. The anhydride oligomers have a molecular weight less than about 5000, typically between about 100 and 5000 daltons, or are defined as including between one to about 20 diacid units linked by anhydride bonds. In one embodiment, the diacids are those normally found in the Krebs glycolysis cycle. The anhydride oligomer compounds have high chemical reactivity.

The oligomers can be formed in a reflux reaction of the diacid with excess acetic anhydride. The excess acetic anhydride is evaporated under vacuum, and the resulting oligomer, which is a mixture of species which include between about one to twenty diacid units linked by anhydride bonds, is purified by recrystallizing, for example from toluene or other organic solvents. The oligomer is collected by filtration, and washed, for example, in ethers. The reaction produces anhydride oligomers of mono and poly acids with terminal carboxylic acid groups linked to each other by anhydride linkages.

The anhydride oligomer is hydrolytically labile. As analyzed by gel permeation chromatography, the molecular weight may be, for example, on the order of 200-400 for fumaric acid oligomer (FAPP) and 2000-4000 for sebacic acid oligomer (SAPP). The anhydride bonds can

be detected by Fourier transform infrared spectroscopy by the characteristic double peak at 1750 cm^{-1} and 1820 cm^{-1}, with a corresponding disappearance of the carboxylic acid peak normally at 1700 cm^{-1}.

In one embodiment, the oligomers may be made from diacids described for example in U.S. Patent No. 4,757,128 to Domb et al., U.S. Patent No. 4,997,904 to Domb, and U.S. Patent No. 5,175,235 to Domb et al., the disclosures of which are incorporated herein by reference. For example, monomers such as sebacic acid, bis(p-carboxy-phenoxy)propane, isophathalic acid, fumaric acid, maleic acid, adipic acid or dodecanedioic acid may be used.

Organic dyes, because of their electronic charge and hydrophilicity/hydrophobicity, may alter the bioadhesive properties of a variety of polymers when incorporated into the polymer matrix or bound to the surface of the polymer. A partial listing of dyes that affect bioadhesive properties include, but are not limited to: acid fuchsin, alcian blue, alizarin red s, auramine o, azure a and b, Bismarck brown y, brilliant cresyl blue ald, brilliant green, carmine, cibacron blue 3GA, congo red, cresyl violet acetate, crystal violet, eosin b, eosin y, erythrosin b, fast green fcf, giemsa, hematoylin, indigo carmine, Janus green b, Jenner's stain, malachite green oxalate, methyl blue, methylene blue, methyl green, methyl violet 2b, neutral red, Nile blue a, orange II, orange G, orcein, paraosaniline chloride, phloxine b, pyronin b and y, reactive blue 4 and 72, reactive brown 10, reactive green 5 and 19, reactive red 120, reactive yellow 2,3, 13 and 86, rose bengal, safranin o, Sudan III and IV, Sudan black B and toluidine blue.

Lipids (and even liposomes) may be used to prepare the flakes used in the present invention. The lipids used may be of either natural, synthetic or semi-synthetic origin. Lipids can be esters of fatty acids, triglycerides, cholesterol esters and vitamin A and D esters. Compound lipids can be phospholipids, glycolipids (cerebrosides), sulfolipids, lipoproteins and lipopolysaccharides. Derived lipids can be saturated and unsaturated fatty acids and mono or diglycerides. Analogs of these lipids can also be used. Lipids include but are not limited to: fatty acids, lysolipids, phosphatidylcholine with both saturated and unsaturated lipids including dioleoylphosphatidylcholine; dimyristoylphosphatidylcholine;dipentadecanoylphosphatidylcholine;dilauroylphosphatidylcholine; dipalmitoylphosphatidylcholine (DPPC); distearoylphosphatidylcholine (DSPC); phosphatidylethanolamines such as dioleoylphosphatidylethanolamine and dipalmitoylphosphatidylethanolamine (DPPE); phosphatidylserine; phosphatidylglycerol; phosphatidylinositol; sphingolipids such as sphingomyelin; glycolipids such as ganglioside GM1 and GM2; glucolipids; sulfatides; glycosphingolipids; phosphatidic acids such as

dipalymitoylphosphatidic acid (DPPA); palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers such as polyethyleneglycol, i.e., PEGylated lipids, chitin, hyaluronic acid or polyvinylpyrrolidone; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides; cholesterol, cholesterol sulfate and cholesterol hemisuccinate; tocopherol hemisuccinate; lipids with ether and ester-linked fatty acids; polymerized lipids (a wide variety of which are well known in the art); diacetyl phosphate; dicetyl phosphate; stearylamine; cardiolipin; phospholipids with short chain fatty acids of 6-8 carbons in length; synthetic phospholipids with asymmetric acyl chains (e.g., with one acyl chain of 6 carbons and another acyl chain of 12 carbons); ceramides.

Fatty acids also can be used in the manufacture of flakes. Fatty acids are carboxylic acid compounds found in animal and vegetable fat and oil. Fatty acids are classified as lipids and are composed of chains of alkyl groups containing from 4 to 22 carbon atoms and 0-6 double bonds and characterized by a terminal carboxyl group, -COOH. Fatty acids may be saturated or unsaturated and may be solid, semisolid, or liquid. The most common saturated fatty acids are butyric acid (C4), lauric acid (C12), palmitic acid (C16), and stearic acid (C18). Unsaturated fatty acids are usually derived from vegetables and consist of alkyl chains containing from 16 to 22 carbon atoms and 0-3 double bonds with the characteristic terminal carboxyl group. The most common unsaturated fatty acids are oleic acid, linoleic acid, and linolenic acid (all C18 acids).

Waxes can also be used to form the flakes of the invention. In general, waxes are long chain fatty alcohol esters of fatty acids. Many waxes have suitable melting characteristics for use in the compositions of the invention, since they are solids at 25°C. Examples include animal waxes, vegetable waxes, petroleum waxes, synthetic waxes, and mixtures thereof and include without limitation beeswax, lanolin, candelilla wax, caranda wax, carnauba wax, microcrystalline wax, carbowax, and mixtures thereof. Preferred waxes are made from saturated or monounsaturated fatty acids and saturated or unsaturated fatty alcohols. An example of the latter is provided by arachidyl oleate.

Excipients useful to manufacture solid oral dosage forms are given as follows: anticaking agents, antioxidants, binders, buffering agents, cellulose, disintegrants, gum, lubricants, glidants, granulating agents, paraffin, plasticizers, polyethylene glycol, solubilizing agents, solvents, starch, wetting agents.

In the case where solid oral dosage form is added to a liquid prior to administration, the liquid is often formulated with the following: Acids, antioxidants, buffering agents, cellulose, citric acids, diluents, emulsifying agents, emollients, gum preservatives, sequestering agents, solubilizing

agents, stabilizing agents, stiffening agents, suspending agents, sweetening agents, viscosity-increasing agents, water, wetting agents.

Acids: Alginic, Ascorbic, Benzoic, Citric, Edetic, Fumaric, Hydrochloric, Lactic, Malic, Oleic, Sorbic, Stearic, Tartaric,

Anticaking agents: Colloidal silicon dioxide, Magnesium trisilicate, Talc, Tribasic calcium phosphate

Antioxidants: Alpha tocopherol, Ascorbic acid, Ascorbyl palmitate, Butylated hydroxyanisole, butylated hydroxytoluene, Fumaric acid, Malic acid, Propyl gallate, Sodium ascorbate, Sodium metabisulfite,

Binders: Acacia, Alginic acid, Carbomer, Carboxymethylcellulose sodium, Dextrin, Ethylcellulose, Gelatin, Guar gum, Hydrogenated vegetable oil, type , Hydroxyethyl cellulose, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Liquid glucose, Magnesium aluminum silicate, Maltodextrin, Methylcellulose, Polymethacrylates, Povidone, Pregelaatinized starch, Sodium algniate, Starch, Zein

Buffering Agents: Acidifying agents, alkalizing agents, Citric acid monohydrate, Dibasic sodium phosphate, Potassium citrate, Sodium citrate dihydrate

Coating agents: Carboxymethylcellulose sodium, Carnauba wax, Cellulose acetate phthalate, Cetyl alcohol, Confectioner's sugar, Ethylcellulose, Gelatin, Hydroxyethyl cellulose, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Liquid glucose, Maltodextrin, Methylcellulose, Microcrystalline wax, Polymethacrylates, Polyvinyl alcohol, Shellac, Sucrose, Talc, Titanium dioxide, Zein

Diluents: Calcium carbonate, Calcium sulfate, Compressible sugar, Confectioner's sugar, Dextrates, Dextrin, Dextrose, Dibasic calcium phosphate dihydrate, Glyceryl palmitostearate, Hydrogenated vegetable oil, type I, Kaolin, Lactose, Magnesium carbonate, Magnesium oxide, Maltodextrin, Mannitol, Microcrystalline cellulose, Polymethacrylates, potassium chloride, powdered cellulose, Pregelatinized starch, Sodium chloride, Sorbitol, Starch, Sucrose, Sugar spheres, Talc, Tribasic calcium phosphate

Disintegrants: Alginic acid, Carbosymethylcellulose calcium, Carboxymethylcellulose sodium, Colloidal silicon dioxide, Croscarmellose sodium, Crospovidone, Guar gum, Magnesium aluminum silicate, Methylcellulose, Microcrystalline cellulose, Polacrilin potassium, Powdered cellulose, Pregelatinized starch, Sodium alginate, Sodium starch glycolate, Starch

Emollients: Cetostearyl alcohol, Cetyl esters wax, Cholesterol. Glycerin, Glyceryl monostearate. Isopropyl myristate, Isopropyl palmitate, Lecithin, Light mineral oil, Mineral oil, Mineral oil and lanolin alcohols, Petrolatum, Petrolatum and lanolin alcohols

Emulsifying agents: Acacia, Anionic emulsifying wax, Carbomer, Cetostearyl alcohol, Cetyl alcohol, cholesterol, Diethanolamine, Glyceryl monostearate, Hydrous lanolin, Hydroxyproply cellulose, Lanolin, Lanolin alcohols, Lecithin, Methylcellulose, Mineral oil and lanolin alcohols, Monobasic sodium phosphate, Monoethanolamine, Nonionic emulsifying wax, Oleic acid, Poloxamer, Polyoxyethylene alkyl ethers, Polyoxyethylene castor oil derivatives, Polyoxyethylene sorbitan fatty acid ester, Polyoxyethylene stearates, Propylene glycol alginate, Sodium lauryl sulfate, Sorbitan esters, Stearic acid, Triethanolamine

Granulating agents: Acacia, Dextrose, Gelatin, Povidone, Starch, Sucrose, Tragacanth

Gum: Acacia, Arabic, Dragon, Guar, Hog, Talha, Tragacanth

Lubricants: Calcium stearate, Glyceryl monostearate, Glyceryl palmitostearate, Hydrogenated castor oil, Hydrogenated vegetable oil, Light mineral oil, Magnesium stearate, Mineral oil, Polyethylene glycol, Sodium benzoate, sodium lauryl sulfate, Sodium stearyl fumarate, Stearic acid, Talc, Zinc stearate

Paraffin

Plasticizers: Benzyl benzoate, Chlorobutanol, Dibutyl sebacate, Diethyl phthalate, glycerin, Mineral oil and lanolin alcohols, Petrolatum and lanolin alcohols, Polyethylene glycol, Propylene glycol, Sorbitol, Triacetin, Triethyl citrate

Preservatives: Alcohol, Benzalkonium chloride, Benzethonium chloride, Benzoic acid, Benzyl alcohol, Bronopol, Butylparaben, Cetrimide, Chlorhexidine, Chlorobutanol, Chlorocresol, Cresol, Ethylparaben, Glycerin, Imidurea, Methylparaben, Phenol, Phenoxyethanol, Phenylethyl alcohol, Phenylmercuric acetate, Phenylmercuric borate, Phenylmercuric nitrate, Potassium sorbate, Propylene glycol, Propylparaben, Sodium benzoate, Sodium propionate, Sorbic acid, Thimerosal

Sequestering Agents: Dibasic sodium phosphate, Monobasic sodium phosphate, Potassium citrate, Sodium citrate dihydrate, Tartaric acid

Solubilizing Agents: Benzalkonium chloride, Benzethonium chloride, Benzyl benzoate, cyclodextrins, Glyceryl monostearate, Lecithin, Poloxamer, Polyoxyethylene alkyl ethers, Polyoxyethylene caster oil

derivatives. Polyoxyethylene sorbitan fatty acid esters, Polyoxyethylene stearates, Sorbitan esters, Stearic acid

Stabilizing Agents:

Ethylenebis(iminodiacetic acid), Ethylenediaminetetraacetic acid, Ethylenediaminetetraacetic acid, [(Ethylenedinitrilo)tetraacetato]calciate(2-)disodium, (Ethylenedinitrilo)tetraacetic acid.

Starch: Cassava, Corn, Gum, Maize, Potato, Pregelatinized, Rice, Sterilizable, Sugar, Syrup, Tapioca, Wheat

Stiffening Agents: Anionic emulsifying wax, Cetyl alcohol, Cetyl esters wax, Hydrogenated castor oil, Microcrystalline wax, Nonionic emulsifying wax, Paraffin, Stearyl alcohol, White wax, Yellow wax

Suspending Agents:Acacia, Bentonite, Carbomer, Carboxymethylcellulose calcium, Carboxymethylcellulose sodium, Colloidal silicon dioxide, Dextrin, Gelatin, Guar gum, Hydroxyethyl cellulose, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Kaolin, Magnesium aluminum silicate, Maltitol solution, Methylcellulose, Microcrystalline cellulose, Povidone, Powdered cellulose, Propylene glycol alginate, Sodium alginate, Sodium starch glycolate, Starch, Sucrose, Tragacanth, Xantham gum

Sweetening Agents: Bulk: Compressible sugar, Confectioner's sugar, Dextrose, Glycerin, Lactose, Liquid glucose, Maltitol solution, Mannitol, Sorbitol, Sucrose, Xylitol
Intense: Acesulfame potassium, Aspartame, Saccharine, Saccharin sodium, Sodium cyclamate

Viscosity-increasing Agents: acacia, Alginic acid, Bentonite, Carbomer, Carboxymethylcellulose calcium, Carboxymethylcellulose sodium, Cetostearyl alcohol, Colloidal silicon dioxide, Ethylcellulose, Gelatin, Guar gum, Hydroxyethyl cellulose, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Magnesium aluminum silicate, Maltodextrin, Methylcellulose, Polyvinyl alcohol, Povidone, Propylene carbonate, Propylene glycol alginate, Sodium alginate, Sodium starch glycolate, Starch Sucrose, Tragacanth, Xanthan gum

The flakes according to the invention can be manufactured according to many well known methodologies. The flakes may be cast, such as by drum casting or bell casting. The flakes may be fractured, chipped or shaved from solid materials. The flakes may be pressed, stamped or embossed by conventional equipment. Likewise, the flakes may be milled such as using a roller milling

apparatus. The flakes also may be extruded such as in the form of a ribbon which is broken into smaller pieces. The flakes also may be rolled from wet particulates. Methods of producing flakes are well-known to those of ordinary skill in the art. See, for example, U.S. Patent Nos. 4,107,344, 4,116,601, 4,550,003, 4,253,993.

One embodiment of an apparatus according to the invention is depicted in Fig. 1. The apparatus includes a turntable (1) which allows transport of the rotor head (2) in a rotary fashion. The turntable also can be used to collect flake product. The rotor head (2) is a stainless steel cylinder upon which can be sprayed solutions of excipients, drugs, coatings and the like. The drum can be heated and the solutions, upon drying, will form a thin film on the rotating surface. The rotor head (2) can be heated using a radiant heat source. The rotor head (2) is mounted on the turntable (1). A spray head system (3) is used to deliver fluid as a fine spray onto the rotor head (2). The spray head system uses compressed gas to generate a fine mist. A wiper arm (4) is used to remove the dried material from the rotor head. The wiper arm (4) can be a steel razor that contacts the rotor head to scrape the flakes from the rotor head. The wiper arm is attached to a wiper arm tension control mechanism (5) which can be an elastic band used to control tension on the wiper arm against the rotor head. A radiant heat source (6) can be used to heat the rotor head and dry the materials spayed upon the rotor head.

Flake technology is analogous to nano and microparticulate or granular drug morphologies in that most forms are amenable to direct processing as matrix composition, meaning active drug substance is embedded into a soluble or insoluble matrix which modifies the release characteristics of the drug. They are also amenable to further processing to generate taste masked and sustained or controlled release. This is done through the use and application of single or multiple layers of coatings. Each layer is applied in such a way a to engineer the desired properties into the coated drug.

Coatings are comprised of natural waxes or polymers, chemically or physically modified waxes or polymers, and totally synthetic polymers. The chemical modifications to natural waxes and polymers impart desirable characteristics to the materials. The totally synthetic polymers are constructed to possess the desired characteristics. These characteristics are differential solubility of the polymer or wax at different temperatures, pH, ionic strength, and solvent composition. One skilled in the art is familiar with these characteristics and materials and reference is given to "Handbook of Pharmaceutical Excipients", 2nd ed, A. Wade and P.J. Weller, eds., 1994, APA, Washington, The Pharmaceutical Press, London.

Coating of particulate is normally accomplished using readily available commercial processing equipment designed for this task. The equipment normally involves a means of suspending or otherwise mixing the particulate, a means of applying the coating using a spraying device and auxiliary air which can be heated, and other support equipment related to conditioning of air, environmental control, and recovery of materials. These coating devices either spray coating liquid from below or above and suspend particulate by revolving, as in a drum coater, or being static and suspending the particulate from below using air. Anyone skilled in the art is familiar with these spray dryers and tablet coaters.

Coatings are applied to particulate systems, tablets, caplets and other dosage forms to modify both the release characteristics of the drug substance and protect the drug substance from the environment. This is done for a variety of reasons not limited to the following. Dosage forms may be hygroscopic and need to be coated with a wax or other water barrier to prevent the intrusion of water into the dosage form. Dosage forms may have high solubility and undesirable taste and require taste masking using a coating that will not dissolve in the mouth but will only dissolve at a pH above approximately 6.0. Dosage forms may require frequent dosing and therefore it is desirable to develop a dosage form with sustained release characteristics. This can be accomplished using a coating, which partially dissolves at a neutral pH and acts a diffusion barrier to the drug substance. Additionally, the drug substance is often embedded in an insoluble matrix, which in itself acts as a diffusion barrier. Drug substance may be specifically targeted for absorption in a particular part of the digestive track. In this case the drug substance is coated with a material that will only dissolve at a relatively high pH, for example above 7.0.

These coating principles and the use of various matrixes for modifying the release characteristics of a drug substance have been successfully applied to nanoparticles, microparticles, multipleunit dosage forms, meaning a single dosage form comprised of multiple subunits such as individual tablets, resin based drug delivery devices, tablets, capsules, caplets, pills, and variations and compilation of all of these. The technical aspect of developing immediate, sustained and controlled release drug substances is well known to anyone skilled in the art. ["Practical Course in Film Coatings of Pharmaceutical Dosage Forms with EUDRAGIT®", Dr. Klaus Lehmann, Rohm Pharma Polymers, 1996]

Coatings used for modifying the release characteristics and protecting a drug substance from the environment are well-known to those of ordinary skill in the art. The coatings can be made from any of the materials described above for manufacturing the flake. Well-known "coating agents" are

described below. Suitable enteric coatings for flakes include ethylcellulose, polyvinylchloride, methylcellulose, polyurethane, cellulose acetate, polycarbonate, polyethylene, polypropylene, shellac and polymers of acrylic and methyl acrylic acids and esters of it. Waxes also frequently are used as coating and are described above. Well-known extended release materials used as coatings include bentonite, carbomer, glyceryl palmitostearate, hydrogenated castor oil, polacrilin potassium and zein. Other well-known coatings are the polymethacrylates, including ammonio methacrylate copolymer and methacrylate acid copolymer. A well-known line of polymethacrylates are the eudragits (Rohm Pharma GmbH. Technical Literature: Eudragit, 1990.) These materials are commercially available and are configured so as to provide release in different gastric and intestinal environments, providing film coatings, enteric coatings, sustained release coatings and the like. These materials may be used in spray coating processes.

A spoon-feedable base specially fortified to enhance therapeutic effect is developed. The base can be either modeled after a dietary supplement currently formulated and administered in numerous extended health care facilities throughout the country or developed specifically to enhance the drug.

The Nutritionally Fortified Delivery Vehicle can be administered as a freestanding product as well as in combination with drugs. It can be formulated to consist of a viscosity that will facilitate spoon administration to patients currently unable to swallow tablet, capsules, or liquid dosage forms.

The delivery vehicle can complement the drug. It has been demonstrated that certain carbohydrate-to-protein ratios enhance the effect of dopamine, for example. Thus, it may be formulated to enhance certain desired effects of the administered drugs. It can also complement other dietary issues, for example, addressing complications associated with the administration of narcotics. The uptake of narcotics, such as morphine, causes the inability to produce bowel movement. Also, many patients under morphine treatment cannot swallow solid food. Incorporation the morphine into fortified high fiber base will allow an easy spoon-fed administration of the drug and the ability to enhance bowel movement with dietary fiber. One such formulation could include prune juice, apple juice and bran. Another example is a delivery vehicle fortified with vitamins (C, D, E), flavorings (citric acid, ascorbic acid, menthol, sorbitol, xylitol).

The high occurrence of constipation in the elderly population has necessitated the addition of high fiber as a dietary supplement. Such a base is also suited for elderly patients who need the supplement fiber for regular bowel movement (10g per day). The delivery vehicle may also contain simethicone to reduce flatulation.

The list below describes some modifications for compositions designed to complement treatment of a particular disease state.

Disease State	Delivery Vehicle
Renal failure	certain proteins
Liver disease	certain proteins
Hypermetabolic States	certain proteins, amino acids and vitamins
Lung disease	High fat, low carbohydrate
HIV/AIDS	enriched with specific amino acids and vitamins
Diabetes mellitus	carbohydrates, high fiber
Malabsorption	specific fats

An oral medication delivery system is developed, wherein said container means comprises a dual or multiple chamber container. The container can be a rigid substantially cylindrical tube and said container means includes rupturable membrane means for separating the container into first and second chambers, wherein said pharmaceutically active agent in powder form is disposed within said first chamber and a spoon-feedable, is disposed within said second chamber, removable seal means for sealing said delivery liquid in said second chamber, and plunger means for sealing said pharmaceutically active agent in said first chamber and for rupturing said rupturable membrane to mix said pharmaceutically active agent and said delivery liquid.

While the above examples have addressed the needs of the geriatric population, it will be readily apparent that the invention may be applied to other populations which experience difficulty in taking conventional solid and liquid dosage formats. For example, pediatric, oncology or other patients who cannot swallow will benefit from a spoon-able drug delivery dosage form. Similarly to the elderly, young children cannot handle the swallowing of a tablet and prefer a dosage form that could be spoon-fed to them. Cancer patients who undergo radiation therapy of the head and neck area or take chemotherapeutic drugs experience the lack of formation of saliva and/or esophagitis which results in difficulty taking solid food such as tablets.

Examples of drugs that might be utilized in a delivery application of the invention include any hydrophilic or hydrophobic drug at a concentration for having a therapeutic benefit. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use by the appropriate governmental agency or body. For example, drugs for human use listed by the FDA under 21 C.F.R. 330.5, 331 through 361; 440-460; drugs for veterinary use listed by the FDA under 21 C.F.R. 550-582, incorporated herein by reference, are all considered acceptable for use in the present novel flakes.

The term "drug" includes pharmacologically active substances that produce a local or systemic therapeutic effect in subjects or plants. The term thus means any substance intended for use in the diagnosis, or therapeutic treatment or prevention of disease. The term "subject" used herein is taken to mean humans, nonhuman primates, sheep, horses, cattle, pigs, goats, dogs, and cats. The term "plant" means higher plants (angiosperms, gymnosperms).

The drug can be any type of compound including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, synthetic and biologically engineered analogs thereof and oils. The term "protein" is art-recognized and for purposes of this invention also encompasses peptides. The proteins or peptides may be any biologically active protein or peptide, naturally occurring or synthetic. The drug can be any antigen.

Other agents which can be delivered in the flakes of the invention, include, but are not limited to, pesticides, herbicides, and biocides.

The present invention involves the delivery of drugs for therapeutic treatment of disease states. A variety of conditions may be treated, including but not limited to hypertension, congestive heart failure, myocardial infarction, atherosclerosis, renal failure, pulmonary hypertension, osteoporosis, cancer, arthritis (rheumatoid or osteo), ulcers, diabetes and complications thereof, neurological disorders such as depression, Parkinson's disease, Alzheimer's disease, psychotic disorders such as schizophrenia, pain associated with various conditions, infectious disease such as urinary tract infection, pneumonia, sepsis, HIV infection, hepatitis A, B and C, influenza, restenosis and the like.

The drug can be, but is not limited to:adrenergic agent; adrenocortical steroid; adrenocortical suppressant; aldosterone antagonist; amino acid; anabolic; analeptic; analgesic; anesthetic; anorectic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-anemic; anti-anginal; anti-arthritic; anti-asthmatic; anti-atherosclerotic; antibacterial; anticholinergic; anticoagulant; anticonvulsant; antidepressant; antidiabetic; antidiarrheal; antidiuretic; anti-emetic; anti-epileptic; antifibrinolytic; antifungal; antihemorrhagic; antihistamine; antihyperlipidemia; antihypertensive; antihypotensive; anti-infective; anti-inflammatory; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiparasitic; antiproliferative; antipsychotic; antirheumatic; antiseborrheic; antisecretory; antispasmodic; antithrombotic; anti-ulcerative; antiviral; appetite suppressant; blood glucose regulator; bone resorption inhibitor; bronchodilator; cardiovascular agent; cholinergic; depressant; diagnostic aid; diuretic; dopaminergic agent; estrogen receptor agonist; fibrinolytic; fluorescent agent; free oxygen radical scavenger;

gastric acid suppressant; gastrointestinal motility effector; glucocorticoid; hair growth stimulant; hemostatic; histamine H2 receptor antagonists; hormone; hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; keratolytic; LHRH agonist; mood regulator; mucolytic; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective; NMDA antagonist; non-hormonal sterol derivative; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; psychotropic; radioactive agent; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine A1 antagonist; serotonin antagonist; serotonin inhibitor; serotonin receptor antagonist; steroid; thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; amyotrophic lateral sclerosis agent; cerebral ischemia agent; Paget's disease agent; unstable angina agent; vasoconstrictor; vasodilator; wound healing agent; xanthine oxidase inhibitor.

Examples include:

Adrenergic: Adrenalone; Amidephrine Mesylate; Apraclonidine Hydrochloride; Brimonidine Tartrate; Dapiprazole Hydrochloride; Deterenol Hydrochloride; Dipivefrin; Dopamine Hydrochloride; Ephedrine Sulfate; Epinephrine; Epinephrine Bitartrate; Epinephryl Borate; Esproquin Hydrochloride; Etafedrine Hydrochloride; Hydroxyamphetamine Hydrobromide; Levonordefrin; Mephentermine Sulfate; Metaraminol Bitartrate; Metizoline Hydrochloride; Naphazoline Hydrochloride; Norepinephrine Bitartrate; Oxidopamine; Oxymetazoline Hydrochloride; Phenylephrine Hydrochloride; Phenylpropanolamine Hydrochloride; Phenylpropanolamine Polistirex; Prenalterol Hydrochloride; Propylhexedrine; Pseudoephedrine Hydrochloride; Tetrahydrozoline Hydrochloride; Tramazoline Hydrochloride; Xylometazoline Hydrochloride.

Adrenocortical steroid: Ciprocinonide; Desoxycorticosterone Acetate; Desoxycorticosterone Pivalate; Dexamethasone Acetate; Fludrocortisone Acetate; Flumoxonide; Hydrocortisone Hemisuccinate; Methylprednisolone Hemisuccinate; Naflocort; Procinonide; Timobesone Acetate; Tipredane.

Adrenocortical suppressant: Aminoglutethimide; Trilostane.

Alcohol deterrent: Disulfiram.

Aldosterone antagonist: Canrenoate Potassium; Canrenone; Dicirenone; Mexrenoate Potassium; Prorenoate Potassium; Spironolactone.

Amino acid: Alanine; Arginine; Aspartic Acid; Carnitine; Cysteine Hydrochloride; Cystine; Glycine; Histidine; Isoleucine; Leucine; Lysine; Lysine Acetate; Lysine Hydrochloride; Methionine; Phenylalanine; Proline; Serine; Threonine; Tryptophan; Tyrosine; Valine.

Ammonia detoxicant: Arginine: Arginine Glutamate; Arginine Hydrochloride.

Anabolic: Bolandiol Dipropionate; Bolasterone; Boldenone Undecylenate; Bolenol; Bolmantalate; Ethylestrenol; Methenolone Acetate; Methenolone Enanthate; Mibolerone; Nandrolone Cyclotate; Norbolethone; Pizotyline; Quinbolone; Stenbolone Acetate; Tibolone; Zeranol.

Analeptic: Modafinil.

Analgesic: Acetaminophen; Alfentanil Hydrochloride; Aminobenzoate Potassium; Aminobenzoate Sodium; Anidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzydamine Hydrochloride; Bicifadine Hydrochloride; Brifentanil Hydrochloride; Bromadoline Maleate; Bromfenac Sodium; Buprenorphine Hydrochloride; Butacetin; Butixirate; Butorphanol; Butorphanol Tartrate; Carbamazepine; Carbaspirin Calcium; Carbiphene Hydrochloride; Carfentanil Citrate; Ciprefadol Succinate; Ciramadol; Ciramadol Hydrochloride; Clonixeril; Clonixin; Codeine ; Codeine Phosphate; Codeine Sulfate; Conorphone Hydrochloride; Cyclazocine; Dexoxadrol Hydrochloride; Dexpemedolac; Dezocine; Diflunisal; Dihydrocodeine Bitartrate; Dimefadane; Dipyrone; Doxpicomine Hydrochloride; Drinidene; Enadoline Hydrochloride; Epirizole; Ergotamine Tartrate; Ethoxazene Hydrochloride; Etofenamate; Eugenol; Fenoprofen; Fenoprofen Calcium; Fentanyl Citrate; Floctafenine; Flufenisal; Flunixin; Flunixin Meglumine; Flupirtine Maleate; Fluproquazone; Fluradoline Hydrochloride; Flurbiprofen ; Hydromorphone Hydrochloride; Ibufenac; Indoprofen; Ketazocine; Ketorfanol; Ketorolac Tromethamine; Letimide Hydrochloride; Levomethadyl Acetate; Levomethadyl Acetate Hydrochloride; Levonantradol Hydrochloride; Levorphanol Tartrate; Lofemizole Hydrochloride; Lofentanil Oxalate; Lorcinadol; Lornoxicam; Magnesium Salicylate; Mefenamic Acid; Menabitan Hydrochloride; Meperidine Hydrochloride; Meptazinol Hydrochloride; Methadone Hydrochloride; Methadyl Acetate; Methopholine; Methotrimeprazine; Metkephamid

Acetate; Mimbane Hydrochloride; Mirfentanil Hydrochloride; Molinazone; Morphine Sulfate; Moxazocine; Nabitan Hydrochloride; Nalbuphine Hydrochloride; Nalmexone Hydrochloride ; Namoxyrate; Nantradol Hydrochloride; Naproxen ; Naproxen Sodium ; Naproxol; Nefopam Hydrochloride; Nexeridine Hydrochloride; Noracymethadol Hydrochloride; Ocfentanil Hydrochloride; Octazamide; Olvanil; Oxetorone Fumarate; Oxycodone; Oxycodone Hydrochloride; Oxycodone Terephthalate; Oxymorphone Hydrochloride; Pemedolac; Pentamorphone; Pentazocine; Pentazocine Hydrochloride; Pentazocine Lactate; Phenazopyridine Hydrochloride; Phenyramidol Hydrochloride; Picenadol Hydrochloride; Pinadoline; Pirfenidone; Piroxicam Olamine; Pravadoline Maleate; Prodilidine Hydrochloride; Profadol Hydrochloride; Propiram Fumarate; Propoxyphene Hydrochloride; Propoxyphene Napsylate; Proxazole ; Proxazole Citrate ; Proxorphan Tartrate; Pyrroliphene Hydrochloride; Remifentanil Hydrochloride; Salcolex ; Salethamide Maleate; Salicylamide; Salicylate Meglumine; Salsalate ; Sodium Salicylate; Spiradoline Mesylate; Sufentanil; Sufentanil Citrate; Talmetacin ; Talniflumate ; Talosalate ; Tazadolene Succinate; Tebufelone ; Tetrydamine ; Tifurac Sodium; Tilidine Hydrochloride; Tiopinac; Tonazocine Mesylate; Tramadol Hydrochloride; Trefentanil Hydrochloride; Trolamine; Veradoline Hydrochloride; Verilopam Hydrochloride; Volazocine; Xorphanol Mesylate; Xylazine Hydrochloride; Zenazocine Mesylate; Zomepirac Sodium ; Zucapsaicin.

Androgen: Fluoxymesterone; Mesterolone; Methyltestosterone; Nandrolone Decanoate; Nandrolone Phenpropionate; Nisterime Acetate; Oxandrolone; Oxymetholone; Silandrone; Stanozolol; Testosterone; Testosterone Cypionate; Testosterone Enanthate; Testosterone Ketolaurate; Testosterone Phenylacetate; Testosterone Propionate; Trestolone Acetate.

Anesthesia, adjunct to: Sodium Oxybate.

Anesthetic: Aliflurane; Benoxinate Hydrochloride; Benzocaine; Biphenamine Hydrochloride ; Bupivacaine Hydrochloride; Butamben; Butamben Picrate; Chloroprocaine Hydrochloride; Cocaine; Cocaine Hydrochloride; Cyclopropane; Desflurane; Dexivacaine; Diamocaine Cyclamate; Dibucaine; Dibucaine Hydrochloride; Dyclonine Hydrochloride; Enflurane; Ether; Ethyl Chloride; Etidocaine; Etoxadrol Hydrochloride; Euprocin Hydrochloride; Fluroxene; Halothane; Isobutamben; Isoflurane; Ketamine Hydrochloride; Levoxadrol Hydrochloride ; Lidocaine; Lidocaine Hydrochloride; Mepivacaine Hydrochloride; Methohexital Sodium; Methoxyflurane; Midazolam

Hydrochloride; Midazolam Maleate; Minaxolone; Norflurane; Octodrine; Oxethazaine; Phencyclidine Hydrochloride; Pramoxine Hydrochloride; Prilocaine Hydrochloride; Procaine Hydrochloride; Propanidid; Proparacaine Hydrochloride; Propofol; Propoxycaine Hydrochloride; Pyrrocaine; Risocaine; Rodocaine; Roflurane; Salicyl Alcohol; Sevoflurane; Teflurane; Tetracaine; Tetracaine Hydrochloride; Thiamylal; Thiamylal Sodium; Thiopental Sodium ; Tiletamine Hydrochloride; Zolamine Hydrochloride.

Anorectic compounds including dexfenfluramine.

Anorexic: Aminorex; Amphecloral; Chlorphentermine Hydrochloride; Clominorex; Clortermine Hydrochloride; Diethylpropion Hydrochloride; Fenfluramine Hydrochloride; Fenisorex; Fludorex; Fluminorex; Levamfetamine Succinate; Mazindol; Mefenorex Hydrochloride; Phenmetrazine Hydrochloride; Phentermine; Sibutramine Hydrochloride.

Antagonist: Atipamezole; Atosiban; Bosentan; Cimetidine; Cimetidine Hydrochloride; Clentiazem Maleate; Detirelix Acetate; Devazepide; Donetidine; Etintidine Hydrochloride ; Famotidine; Fenmetozole Hydrochloride ; Flumazenil; Icatibant Acetate; Icotidine; Isradipine; Metiamide; Nadide; Nalmefene; Nalmexone Hydrochloride ; Naloxone Hydrochloride; Naltrexone; Nilvadipine; Oxilorphan; Oxmetidine Hydrochloride ; Oxmetidine Mesylate ; Quadazocine Mesylate; Ranitidine; Ranitidine Bismuth Citrate ; Ranitidine Hydrochloride ; Sufotidine; Teludipine Hydrochloride; Tiapamil Hydrochloride; Tiotidine; Vapiprost Hydrochloride; Zaltidine Hydrochloride.

Anterior pituitary activator: Epimestrol.

Anterior pituitary suppressant: Danazol.

Anthelmintic: Albendazole; Anthelmycin; Bromoxanide; Bunamidine Hydrochloride; Butonate; Cambendazole; Carbantel Lauryl Sulfate; Clioxanide; Closantel; Cyclobendazole; Dichlorvos; Diethylcarbamazine Citrate; Dribendazole; Dymanthine Hydrochloride; Etibendazole; Fenbendazole; Furodazole; Hexylresorcinol; Mebendazole; Morantel Tartrate; Niclosamide; Nitramisole Hydrochloride; Nitrodan; Oxantel Pamoate; Oxfendazole; Oxibendazole; Parbendazole; Piperamide Maleate; Piperazine; Piperazine Citrate; Piperazine Edetate Calcium; Proclonol; Pyrantel

Pamoate; Pyrantel Tartrate; Pyrvinium Pamoate; Rafoxanide; Stilbazium Iodide; Tetramisole Hydrochloride; Thiabendazole; Ticarbodine; Tioxidazole; Triclofenol Piperazine; Vincofos; Zilantel.

Anti-acne: Adapalene; Erythromycin Salnacedin; Inocoterone Acetate.

Anti-adrenergic: Acebutolol; Alprenolol Hydrochloride; Atenolol; Bretylium Tosylate; Bunolol Hydrochloride; Carteolol Hydrochloride; Celiprolol Hydrochloride; Cetamolol Hydrochloride; Cicloprolol Hydrochloride; Dexpropranolol Hydrochloride; Diacetolol Hydrochloride; Dihydroergotamine Mesylate; Dilevalol Hydrochloride; Esmolol Hydrochloride; Exaprolol Hydrochloride; Fenspiride Hydrochloride; Flestolol Sulfate; Labetalol Hydrochloride ; Levobetaxolol Hydrochloride; Levobunolol Hydrochloride; Metalol Hydrochloride; Metoprolol; Metoprolol Tartrate; Nadolol; Pamatolol Sulfate; Penbutolol Sulfate; Phentolamine Mesylate; Practolol; Propranolol Hydrochloride; Proroxan Hydrochloride; Solypertine Tartrate; Sotalol Hydrochloride; Timolol; Timolol Maleate; Tiprenolol Hydrochloride; Tolamolol; Zolertine Hydrochloride.

Anti-allergic: Amlexanox; Astemizole; Azelastine Hydrochloride; Eclazolast ; Minocromil ; Nedocromil ; Nedocromil Calcium ; Nedocromil Sodium ; Nivimedone Sodium; Pemirolast Potassium ; Pentigetide; Pirquinozol; Poisonoak Extract; Probicromil Calcium; Proxicromil; Repirinast ; Tetrazolast Meglumine; Thiazinamium Chloride; Tiacrilast; Tiacrilast Sodium; Tiprinast Meglumine; Tixanox.

Anti-amebic : Berythromycin ; Bialamicol Hydrochloride; Chloroquine; Chloroquine Hydrochloride; Chloroquine Phosphate ; Clamoxyquin Hydrochloride; Clioquinol ; Emetine Hydrochloride; Iodoquinol; Paromomycin Sulfate; Quinfamide; Symetine Hydrochloride; Teclozan; Tetracycline ; Tetracycline Hydrochloride.

Anti-androgen: Benorterone; Cioteronel; Cyproterone Acetate; Delmadinone Acetate ; Oxendolone; Topterone; Zanoterone.

Anti-anemic: Epoetin Alfa; Epoetin Beta ; Ferrous Sulfate, Dried; Leucovorin Calcium.

Anti-anginal: Amlodipine Besylate; Amlodipine Maleate; Betaxolol Hydrochloride ; Bevantolol Hydrochloride ; Butoprozine Hydrochloride; Carvedilol ; Cinepazet Maleate; Metoprolol Succinate ; Molsidomine ; Monatepil Maleate; Primidolol ; Ranolazine Hydrochloride; Tosifen; Verapamil Hydrochloride.

Anti-anxiety agent: Adatanserin Hydrochloride; Alpidem; Binospirone Mesylate; Bretazenil; Glemanserin; Ipsapirone Hydrochloride; Mirisetron Maleate; Ocinaplon; Ondansetron Hydrochloride ; Panadiplon; Pancopride ; Pazinaclone; Serazapine Hydrochloride; Tandospirone Citrate; Zalospirone Hydrochloride.

Anti-arthritic: Lodelaben .

Anti-asthmatic: Ablukast; Ablukast Sodium; Azelastine Hydrochloride ; Bunaprolast; Cinalukast; Cromitrile Sodium; Cromolyn Sodium; Enofelast; Isamoxole; Ketotifen Fumarate; Levcromakalim; Lodoxamide Ethyl ; Lodoxamide Tromethamine; Montelukast Sodium; Ontazolast; Oxarbazole; Oxatomide; Piriprost; Piriprost Potassium; Pirolate; Pobilukast Edamine; Quazolast ; Repirinast ; Ritolukast; Sulukast; Tetrazolast Meglumine ; Tiaramide Hydrochloride; Tibenelast Sodium ; Tomelukast; Tranilast; Verlukast; Verofylline ; Zarirlukast.

Anti-atherosclerotic: Mifobate; Timefuronc.

Antibacterial: Acedapsone ; Acetosulfone Sodium; Alamecin; Alexidine; Amdinocillin; Amdinocillin Pivoxil; Amicycline; Amifloxacin; Amifloxacin Mesylate; Amikacin; Amikacin Sulfate; Aminosalicylic acid; Aminosalicylate sodium; Amoxicillin; Amphomycin; Ampicillin; Ampicillin Sodium; Apalcillin Sodium; Apramycin; Aspartocin; Astromicin Sulfate; Avilamycin; Avoparcin; Azithromycin; Azlocillin; Azlocillin Sodium; Bacampicillin Hydrochloride; Bacitracin; Bacitracin Methylene Disalicylate; Bacitracin Zinc; Bambermycins; Benzoylpas Calcium; Berythromycin ; Betamicin Sulfate; Biapenem; Biniramycin; Biphenamine Hydrochloride ; Bispyrithione Magsulfex ; Butikacin; Butirosin Sulfate; Capreomycin Sulfate; Carbadox; Carbenicillin Disodium; Carbenicillin Indanyl Sodium; Carbenicillin Phenyl Sodium; Carbenicillin Potassium; Carumonam Sodium; Cefaclor; Cefadroxil; Cefamandole; Cefamandole Nafate; Cefamandole Sodium; Cefaparole; Cefatrizine; Cefazaflur Sodium; Cefazolin; Cefazolin Sodium;

Cefbuperazone: Cefdinir; Cefepime; Cefepime Hydrochloride; Cefetecol; Cefixime; Cefmenoxime Hydrochloride; Cefmetazole; Cefmetazole Sodium; Cefonicid Monosodium; Cefonicid Sodium; Cefoperazone Sodium; Ceforanide; Cefotaxime Sodium; Cefotetan; Cefotetan Disodium; Cefotiam Hydrochloride; Cefoxitin; Cefoxitin Sodium; Cefpimizole; Cefpimizole Sodium; Cefpiramide; Cefpiramide Sodium; Cefpirome Sulfate; Cefpodoxime Proxetil; Cefprozil; Cefroxadine; Cefsulodin Sodium; Ceftazidime; Ceftibuten; Ceftizoxime Sodium; Ceftriaxone Sodium; Cefuroxime; Cefuroxime Axetil; Cefuroxime Pivoxetil; Cefuroxime Sodium; Cephacetrile Sodium; Cephalexin; Cephalexin Hydrochloride; Cephaloglycin; Cephaloridine; Cephalothin Sodium; Cephapirin Sodium; Cephradine; Cetocycline Hydrochloride; Cetophenicol; Chloramphenicol; Chloramphenicol Palmitate; Chloramphenicol Pantothenate Complex ; Chloramphenicol Sodium Succinate; Chlorhexidine Phosphanilate; Chloroxylenol; Chlortetracycline Bisulfate ; Chlortetracycline Hydrochloride ; Cinoxacin; Ciprofloxacin; Ciprofloxacin Hydrochloride; Cirolemycin ; Clarithromycin; Clinafloxacin Hydrochloride; Clindamycin; Clindamycin Hydrochloride; Clindamycin Palmitate Hydrochloride; Clindamycin Phosphate; Clofazimine ; Cloxacillin Benzathine; Cloxacillin Sodium; Cloxyquin; Colistimethate Sodium; Colistin Sulfate; Coumermycin; Coumermycin Sodium; Cyclacillin; Cycloserine; Dalfopristin; Dapsone ; Daptomycin; Demeclocycline; Demeclocycline Hydrochloride; Demecycline; Denofungin ; Diaveridine; Dicloxacillin; Dicloxacillin Sodium; Dihydrostreptomycin Sulfate; Dipyrithione; Dirithromycin; Doxycycline; Doxycycline Calcium ; Doxycycline Fosfatex; Doxycycline Hyclate; Droxacin Sodium; Enoxacin; Epicillin; Epitetracycline Hydrochloride; Erythromycin; Erythromycin Acistrate; Erythromycin Estolate; Erythromycin Ethylsuccinate; Erythromycin Gluceptate; Erythromycin Lactobionate; Erythromycin Propionate; Erythromycin Stearate; Ethambutol Hydrochloride; Ethionamide; Fleroxacin; Floxacillin; Fludalanine; Flumequine; Fosfomycin; Fosfomycin Tromethamine; Fumoxicillin; Furazolium Chloride; Furazolium Tartrate; Fusidate Sodium; Fusidic Acid; Gentamicin Sulfate; Gloximonam; Gramicidin; Haloprogin; Hetacillin; Hetacillin Potassium; Hexedine; Ibafloxacin; Imipenem; Isoconazole; Isepamicin; Isoniazid; Josamycin; Kanamycin Sulfate; Kitasamycin; Levofuraltadone; Levopropylcillin Potassium; Lexithromycin; Lincomycin; Lincomycin Hydrochloride; Lomefloxacin; Lomefloxacin Hydrochloride; Lomefloxacin Mesylate; Loracarbef; Mafenide; Meclocycline; Meclocycline Sulfosalicylate; Megalomicin Potassium Phosphate; Mequidox; Meropenem; Methacycline; Methacycline Hydrochloride; Methenamine; Methenamine Hippurate; Methenamine Mandelate; Methicillin Sodium; Metioprim; Metronidazole Hydrochloride; Metronidazole Phosphate;

Mezlocillin; Mezlocillin Sodium; Minocycline; Minocycline Hydrochloride; Mirincamycin Hydrochloride ; Monensin ; Monensin Sodium ; Nafcillin Sodium; Nalidixate Sodium; Nalidixic Acid; Natamycin; Nebramycin; Neomycin Palmitate; Neomycin Sulfate; Neomycin Undecylenate ; Netilmicin Sulfate; Neutramycin; Nifuradene; Nifuraldezone; Nifuratel ; Nifuratrone; Nifurdazil; Nifurimide; Nifurpirinol; Nifurquinazol; Nifurthiazole; Nitrocycline; Nitrofurantoin; Nitromide; Norfloxacin; Novobiocin Sodium; Ofloxacin; Ormetoprim; Oxacillin Sodium; Oximonam; Oximonam Sodium; Oxolinic Acid; Oxytetracycline; Oxytetracycline Calcium; Oxytetracycline Hydrochloride; Paldimycin; Parachlorophenol; Paulomycin; Pefloxacin; Pefloxacin Mesylate; Penamecillin; Penicillin G Benzathine; Penicillin G Potassium; Penicillin G Procaine; Penicillin G Sodium; Penicillin V; Penicillin V Benzathine; Penicillin V Hydrabamine; Penicillin V Potassium; Pentizidone Sodium; Phenyl Aminosalicylate; Piperacillin Sodium; Pirbenicillin Sodium; Piridicillin Sodium; Pirlimycin Hydrochloride; Pivampicillin Hydrochloride; Pivampicillin Pamoate; Pivampicillin Probenate; Polymyxin B Sulfate; Porfiromycin ; Propikacin; Pyrazinamide; Pyrithione Zinc; Quindecamine Acetate; Quinupristin; Racephenicol; Ramoplanin; Ranimycin; Relomycin; Repromicin; Rifabutin; Rifametane; Rifamexil; Rifamide; Rifampin; Rifapentine; Rifaximin; Rolitetracycline; Rolitetracycline Nitrate; Rosaramicin; Rosaramicin Butyrate; Rosaramicin Propionate; Rosaramicin Sodium Phosphate; Rosaramicin Stearate; Rosoxacin; Roxarsone; Roxithromycin; Sancycline; Sanfetrinem Sodium; Sarmoxicillin; Sarpicillin; Scopafungin ; Sisomicin; Sisomicin Sulfate; Sparfloxacin; Spectinomycin Hydrochloride; Spiramycin; Stallimycin Hydrochloride; Steffimycin; Streptomycin Sulfate; Streptonicozid; Sulfabenz ; Sulfabenzamide; Sulfacetamide; Sulfacetamide Sodium; Sulfacytine; Sulfadiazine; Sulfadiazine Sodium; Sulfadoxine; Sulfalene; Sulfamerazine; Sulfameter; Sulfamethazine; Sulfamethizole; Sulfamethoxazole; Sulfamonomethoxine; Sulfamoxole; Sulfanilate Zinc; Sulfanitran ; Sulfasalazine; Sulfasomizole; Sulfathiazole; Sulfazamet; Sulfisoxazole; Sulfisoxazole Acetyl; Sulfisoxazole Diolamine; Sulfomyxin; Sulopenem; Sultamicillin; Suncillin Sodium; Talampicillin Hydrochloride; Teicoplanin; Temafloxacin Hydrochloride; Temocillin; Tetracycline; Tetracycline Hydrochloride ; Tetracycline Phosphate Complex; Tetroxoprim; Thiamphenicol; Thiphencillin Potassium; Ticarcillin Cresyl Sodium; Ticarcillin Disodium; Ticarcillin Monosodium; Ticlatone; Tiodonium Chloride; Tobramycin; Tobramycin Sulfate; Tosufloxacin; Trimethoprim; Trimethoprim Sulfate; Trisulfapyrimidines; Troleandomycin; Trospectomycin Sulfate; Tyrothricin; Vancomycin; Vancomycin Hydrochloride; Virginiamycin; Zorbamycin.

Anticholelithic: Monoctanoin.

Anticholelithogenic: Chenodiol; Ursodiol.

Anticholinergic: Alverinc Citrate; Anisotropine Methylbromide; Atropine; Atropine Oxide Hydrochloride; Atropine Sulfate; Belladonna; Benapryzine Hydrochloride; Benzetimide Hydrochloride; Benzilonium Bromide; Biperiden ; Biperiden Hydrochloride; Biperiden Lactate ; Clidinium Bromide; Cyclopentolate Hydrochloride; Dexetimide; Dicyclomine Hydrochloride; Dihexyverine Hydrochloride; Domazoline Fumarate; Elantrine; Elucaine; Ethybenztropine; Eucatropine Hydrochloride; Glycopyrrolate; Heteronium Bromide; Homatropine Hydrobromide; Homatropine Methylbromide; Hyoscyamine; Hyoscyamine Hydrobromide; Hyoscyamine Sulfate; Isopropamide Iodide; Mepenzolate Bromide; Methylatropine Nitrate; Metoquizine; Oxybutynin Chloride; Parapenzolate Bromide; Pentapiperium Methylsulfate; Phencarbamide; Poldine Methylsulfate; Proglumide; Propantheline Bromide; Propenzolate Hydrochloride; Scopolamine Hydrobromide; Tematropium Methylsulfate; Tiquinamide Hydrochloride; Tofenacin Hydrochloride; Toquizine; Triampyzine Sulfate; Trihexyphenidyl Hydrochloride; Tropicamide.

Anticoagulant: Ancrod; Ardeparin Sodium; Bivalirudin ; Bromindione; Dalteparin Sodium ; Desirudin; Dicumarol; Lyapolate Sodium; Nafamostat Mesylate ; Phenprocoumon; Tinzaparin Sodium ; Warfarin Sodium.

Anticoccidal: Maduramicin.

Anticonvulsant: Albutoin; Ameltolide; Atolide; Buramate; Carbamazepine ; Cinromide; Citenamide; Clonazepam; Cyheptamide; Dezinamide; Dimethadione; Divalproex Sodium; Eterobarb; Ethosuximide; Ethotoin; Flurazepam Hydrochloride ; Fluzinamide; Fosphenytoin Sodium; Gabapentin; Ilepcimide; Lamotrigine; Magnesium Sulfate ; Mephenytoin; Mephobarbital ; Methetoin; Methsuximide; Milacemide Hydrochloride ; Nabazenil; Nafimidone Hydrochloride; Nitrazepam ; Phenacemide; Phenobarbital ; Phenobarbital Sodium ; Phensuximide; Phenytoin; Phenytoin Sodium; Primidone; Progabide; Ralitoline; Remacemide Hydrochloride; Ropizine; Sabeluzole ; Stiripentol; Sulthiame; Thiopental Sodium ; Tiletamine Hydrochloride ; Topiramate;

Trimethadione; Valproate Sodium; Valproic Acid; Vigabatrin; Zoniclezole Hydrochloride; Zonisamide.

Antidepressant: Adatanserin Hydrochloride; Adinazolam ; Adinazolam Mesylate; Alaproclate; Aletamine Hydrochloride; Amedalin Hydrochloride; Amitriptyline Hydrochloride; Amoxapine; Aptazapine Maleate; Azaloxan Fumarate; Azepindole; Azipramine Hydrochloride; Bipenamol Hydrochloride; Bupropion Hydrochloride; Butacetin; Butriptyline Hydrochloride; Caroxazone; Cartazolate; Ciclazindol; Cidoxepin Hydrochloride; Cilobamine Mesylate; Clodazon Hydrochloride; Clomipramine Hydrochloride; Cotinine Fumarate; Cyclindole; Cypenamine Hydrochloride; Cyprolidol Hydrochloride; Cyproximide ; Daledalin Tosylate; Dapoxetine Hydrochloride; Dazadrol Maleate; Dazepinil Hydrochloride; Desipramine Hydrochloride; Dexamisole; Deximafen; Dibenzepin Hydrochloride; Dioxadrol Hydrochloride; Dothiepin Hydrochloride; Doxepin Hydrochloride; Duloxetine Hydrochloride; Eclanamine Maleate; Encyprate; Etoperidone Hydrochloride; Fantridone Hydrochloride; Fenmetozole Hydrochloride ; Fenmetramide; Fezolamine Fumarate; Fluotracen Hydrochloride ; Fluoxetine; Fluoxetine Hydrochloride; Fluparoxan Hydrochloride; Gamfexine; Guanoxyfen Sulfate ; Imafen Hydrochloride; Imiloxan Hydrochloride; Imipramine Hydrochloride; Indeloxazine Hydrochloride; Intriptyline Hydrochloride; Iprindole; Isocarboxazid; Ketipramine Fumarate; Lofepramine Hydrochloride; Lortalamine; Maprotiline; Maprotiline Hydrochloride; Melitracen Hydrochloride; Milacemide Hydrochloride; Minaprine Hydrochloride; Mirtazapine; Moclobemide; Modaline Sulfate; Napactadine Hydrochloride; Napamezole Hydrochloride; Nefazodone Hydrochloride; Nisoxetine; Nitrafudam Hydrochloride; Nomifensine Maleate; Nortriptyline Hydrochloride; Octriptyline Phosphate; Opipramol Hydrochloride; Oxaprotiline Hydrochloride; Oxypertine; Paroxetine; Phenelzine Sulfate; Pirandamine Hydrochloride; Pizotyline ; Pridefine Hydrochloride; Prolintane Hydrochloride; Protriptyline Hydrochloride; Quipazine Maleate ; Rolicyprine; Seproxetine Hydrochloride; Sertraline Hydrochloride; Sibutramine Hydrochloride ; Sulpiride; Suritozole; Tametraline Hydrochloride; Tampramine Fumarate; Tandamine Hydrochloride; Thiazesim Hydrochloride; Thozalinone; Tomoxetine Hydrochloride; Trazodone Hydrochloride; Trebenzomine Hydrochloride; Trimipramine; Trimipramine Maleate; Venlafaxine Hydrochloride; Viloxazine Hydrochloride; Zimeldine Hydrochloride; Zometapine.

Antidiabetic: Acetohexamide; Buformin; Butoxamine Hydrochloride ; Camiglibose; Chlorpropamide; Ciglitazone; Englitazone Sodium; Etoformin Hydrochloride; Gliamilide; Glibornuride; Glicetanile Sodium; Gliflumide; Glipizide; Glucagon; Glyburide; Glyhexamide; Glymidine Sodium; Glyoctamide; Glyparamide; Insulin; Insulin, Dalanated; Insulin Human; Insulin Human, Isophane; Insulin Human Zinc; Insulin Human Zinc, Extended; Insulin, Isophane; Insulin Lispro; Insulin, Neutral; Insulin Zinc; Insulin Zinc, Extended; Insulin Zinc, Prompt; Linogliride; Linogliride Fumarate; Metformin; Methyl Palmoxirate; Palmoxirate Sodium; Pioglitazone Hydrochloride; Pirogliride Tartrate; Proinsulin Human; Seglitide Acetate; Tolazamide; Tolbutamide; Tolpyrramide; Troglitazone; Zopolrestat.

Antidiarrheal: Rolgamidine, Diphenoxylate hydrochloride (Lomotil), Metronidazole (Flagyl), Methylprednisolone (Medrol), Sulfasalazine (Azulfidine).

Antidiuretic: Argipressin Tannate; Desmopressin Acetate; Lypressin .

Antidote: Dimercaprol; Edrophonium Chloride; Fomepizole; Leucovorin Calcium ; Levoleucovorin Calcium; Methylene Blue ; Protamine Sulfate.

Antidyskinetic: Selegiline Hydrochloride .

Anti-emetic: Alosetron Hydrochloride; Batanopride Hydrochloride; Bemesetron; Benzquinamide; Chlorpromazine ; Chlorpromazine Hydrochloride ; Clebopride; Cyclizine Hydrochloride; Dimenhydrinate; Diphenidol; Diphenidol Hydrochloride; Diphenidol Pamoate; Dolasetron Mesylate ; Domperidone; Dronabinol; Fludorex; Flumeridone; Galdansetron Hydrochloride; Granisetron; Granisetron Hydrochloride; Lurosetron Mesylate; Meclizine Hydrochloride; Metoclopramide Hydrochloride; Metopimazine; Ondansetron Hydrochloride ; Pancopride; Prochlorperazine; Prochlorperazine Edisylate; Prochlorperazine Maleate ; Promethazine Hydrochloride ; Thiethylperazine; Thiethylperazine Malate; Thiethylperazine Maleate; Trimethobenzamide Hydrochloride; Zacopride Hydrochloride.

Anti-epileptic: Felbamate; Loreclezole; Tolgabide, lamotrigine.

Anti-estrogen: Clometherone; Delmadinone Acetate ; Nafoxidine Hydrochloride; Nitromifene Citrate; Raloxifene Hydrochloride; Tamoxifen Citrate; Toremifene Citrate ; Trioxifene Mesylate.

Antifibrinolytic: Nafamostat Mesylate .

Antifungal: Acrisorcin; Ambruticin; Amphotericin B; Azaconazole; Azaserine; Basifungin; Bifonazole; Biphenamine Hydrochloride ; Bispyrithione Magsulfex ; Butoconazole Nitrate; Calcium Undecylenate; Candicidin; Carbol-Fuchsin; Chlordantoin; Ciclopirox; Ciclopirox Olamine; Cilofungin; Cisconazole; Clotrimazole; Cuprimyxin; Denofungin ; Dipyrithione; Doconazole; Econazole; Econazole Nitrate; Enilconazole; Ethonam Nitrate; Fenticonazole Nitrate; Filipin; Fluconazole; Flucytosine; Fungimycin; Griseofulvin; Hamycin; Isoconazole ; Itraconazole; Kalafungin; Ketoconazole; Lomofungin; Lydimycin; Mepartricin ; Miconazole; Miconazole Nitrate; Monensin ; Monensin Sodium ; Naftifine Hydrochloride; Neomycin Undecylenate ; Nifuratel ; Nifurmerone; Nitralamine Hydrochloride; Nystatin; Octanoic Acid; Orconazole Nitrate; Oxiconazole Nitrate; Oxifungin Hydrochloride; Parconazole Hydrochloride; Partricin ; Potassium Iodide ; Proclonol ; Pyrithione Zinc ; Pyrrolnitrin; Rutamycin; Sanguinarium Chloride ; Saperconazole; Scopafungin ; Selenium Sulfide ; Sinefungin; Sulconazole Nitrate; Terbinafine; Terconazole; Thiram; Ticlatone ; Tioconazole; Tolciclate; Tolindate; Tolnaftate; Triacetin; Triafungin; Undecylenic Acid; Viridofulvin; Zinc Undecylenate; Zinoconazole Hydrochloride.

Antiglaucoma agent : Alprenoxime Hydrochloride ; Colforsin; Dapiprazole Hydrochloride ; Dipivefrin Hydrochloride ; Naboctate Hydrochloride ; Pilocarpine; Pirnabine.

Antihemorrhagic: Poliglusam.

Antihemorrheologic:Phentoxifylline

Antihistaminic: Acrivastine; Antazoline Phosphate; Astemizole ; Azatadine Maleate; Barmastine; Bromodiphenhydramine Hydrochloride; Brompheniramine Maleate; Carbinoxamine Maleate; Cetirizine Hydrochloride; Chlorpheniramine Maleate; Chlorpheniramine Polistirex; Cinnarizine; Clemastine; Clemastine Fumarate; Closiramine Aceturate; Cycliramine Maleate; Cyclizine; Cyproheptadine Hydrochloride ; Dexbrompheniramine Maleate; Dexchlorpheniramine Maleate;

Dimethindene Maleate; Diphenhydramine Citrate; Diphenhydramine Hydrochloride; Dorastine Hydrochloride; Doxylamine Succinate; Ebastine; Fexofenadine HCl; Levocabastine Hydrochloride; Loratadine; Mianserin Hydrochloride ; Noberastine; Orphenadrine Citrate ; Pyrabrom; Pyrilamine Maleate; Pyroxamine Maleate; Rocastine Hydrochloride; Rotoxamine; Tazifylline Hydrochloride; Temelastine; Terfenadine; Tripelennamine Citrate; Tripelennamine Hydrochloride; Triprolidine Hydrochloride; Zolamine Hydrochloride .

Antihyperlipidemic: Cholestyramine Resin ; Clofibrate; Colestipol Hydrochloride; Crilvastatin; Dalvastatin; Dextrothyroxine Sodium; Fluvastatin Sodium ; Gemfibrozil; Lecimibide; Lovastatin ; Niacin ; Pravastatin Sodium; Probucol; Simvastatin; Tiqueside; Xenbucin.

Antihyperlipoproteinemic: Acifran; Beloxamide; Bezafibrate; Boxidine; Butoxamine Hydrochloride; Cetaben Sodium; Ciprofibrate; Gemcadiol; Halofenate ; Lifibrate; Meglutol; Nafenopin; Pimetine Hydrochloride; Theofibrate; Tibric Acid; Treloxinate.

Antihypertensive: Alfuzosin Hydrochloride; Alipamide ; Althiazide; Amiquinsin Hydrochloride; Amlodipine Besylate ; Amlodipine Maleate ; Anaritide Acetate ; Atiprosin Maleate; Belfosdil; Bemitradine; Bendacalol Mesylate; Bendroflumethiazide ; Benzthiazide ; Betaxolol Hydrochloride ; Bethanidine Sulfate; Bevantolol Hydrochloride ; Biclodil Hydrochloride; Bisoprolol; Bisoprolol Fumarate; Bucindolol Hydrochloride; Bupicomide; Buthiazide: Candoxatril; Candoxatrilat; Captopril ; Carvedilol ; Ceronapril; Chlorothiazide Sodium ; Cicletanine; Cilazapril; Clonidine; Clonidine Hydrochloride; Clopamide ; Cyclopenthiazide; Cyclothiazide ; Darodipine ; Debrisoquin Sulfate; Delapril Hydrochloride; Diapamide ; Diazoxide; Dilevalol Hydrochloride ; Diltiazem Hydrochloride; Diltiazem Malate; Ditekiren; Doxazosin Mesylate; Ecadotril; Enalapril Maleate; Enalaprilat; Enalkiren; Endralazine Mesylate; Epithiazide ; Eprosartan; Eprosartan Mesylate; Fenoldopam Mesylate ; Flavodilol Maleate; Flordipine; Flosequinan; Fosinopril Sodium ; Fosinoprilat; Guanabenz; Guanabenz Acetate; Guanacline Sulfate; Guanadrel Sulfate; Guancydine; Guanethidine Monosulfate; Guanethidine Sulfate; Guanfacine Hydrochloride; Guanisoquin Sulfate; Guanoclor Sulfate; Guanoctine Hydrochloride; Guanoxabenz; Guanoxan Sulfate; Guanoxyfen Sulfate ; Hydralazine Hydrochloride; Hydralazine Polistirex; Hydroflumethiazide ; Indacrinone ; Indapamide ; Indolapril Hydrochloride; Indoramin; Indoramin Hydrochloride; Indorenate Hydrochloride; Lacidipine; Leniquinsin; Levcromakalim ; Lisinopril; Lofexidine Hydrochloride;

Losartan Potassium; Losulazine Hydrochloride; Mebutamate; Mecamylamine Hydrochloride; Medroxalol; Medroxalol Hydrochloride; Methalthiazide ; Methyclothiazide ; Methyldopa; Methyldopate Hydrochloride; Metipranolol; Metolazone ; Metoprolol Fumarate; Metoprolol Succinate ; Metyrosine; Minoxidil; Monatepil Maleate ; Muzolimine ; Nebivolol; Nifidipine; Nitrendipine; Ofornine; Pargyline Hydrochloride; Pazoxide; Pelanserin Hydrochloride ; Perindopril Erbumine; Phenoxybenzamine Hydrochloride; Pinacidil; Pivopril; Polythiazide ; Prazosin Hydrochloride; Primidolol ; Prizidilol Hydrochloride; Quinapril Hydrochloride ; Quinaprilat ; Quinazosin Hydrochloride; Quinelorane Hydrochloride ; Quinpirole Hydrochloride; Quinuclium Bromide; Ramipril ; Rauwolfia Serpentina; Reserpine; Saprisartan Potassium; Saralasin Acetate; Sodium Nitroprusside; Sulfinalol Hydrochloride; Tasosartan; Teludipine Hydrochloride ; Temocapril Hydrochloride; Terazosin Hydrochloride; Terlakiren; Tiamenidine; Tiamenidine Hydrochloride; Ticrynafen ; Tinabinol; Tiodazosin; Tipentosin Hydrochloride; Trichlormethiazide ; Trimazosin Hydrochloride; Trimethaphan Camsylate; Trimoxamine Hydrochloride; Tripamide; Xipamide ; Zankiren Hydrochloride; Zofenoprilat Arginine.

Antihypotensive: Ciclafrine Hydrochloride; Midodrine Hydrochloride.

Anti-infective: Difloxacin Hydrochloride ; Lauryl Isoquinolinium Bromide; Moxalactam Disodium; Ornidazole; Pentisomicin; Sarafloxacin Hydrochloride; Protease inhibitors of HIV and other retroviruses; Integrase Inhibitors of HIV and other retroviruses; Cefaclor (Ceclor); Acyclovir (Zovirax); Norfloxacin (Noroxin); Cefoxitin (Mefoxin); Cefuroxime axetil (Ceftin); Ciprofloxacin (Cipro).

Anti-infective, topical: Alcohol; Aminacrine Hydrochloride; Benzethonium Chloride : Bithionolate Sodium; Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridinium Chloride : Chlorhexidine Hydrochloride; Clioquinol ; Domiphen Bromide; Fenticlor; Fludazonium Chloride; Fuchsin, Basic; Furazolidone ; Gentian Violet; Halquinols; Hexachlorophene : Hydrogen Peroxide; Ichthammol; Imidecyl Iodine; Iodine; Isopropyl Alcohol ; Mafenide Acetate; Meralein Sodium; Mercufenol Chloride; Mercury, Ammoniated; Methylbenzethonium Chloride; Nitrofurazone; Nitromersol; Octenidine Hydrochloride; Oxychlorosene; Oxychlorosene Sodium; Parachlorophenol, Camphorated; Potassium Permanganate; Povidone-Iodine; Sepazonium Chloride; Silver Nitrate; Sulfadiazine, Silver; Symclosene; Thimerfonate Sodium; Thimerosal : Troclosene Potassium.

Anti-inflammatory: Alclofenac; Alclometasone Dipropionate; Algestone Acetonide; Alpha Amylase; Amcinafal; Amcinafide; Amfenac Sodium; Amiprilose Hydrochloride; Anakinra; Anirolac ; Anitrazafen; Apazone; Balsalazide Disodium; Bendazac; Benoxaprofen ; Benzydamine Hydrochloride; Bromelains; Broperamole; Budesonide; Carprofen; Ciclopropen; Cintazone; Cliprofen; Clobetasol Propionate; Clobetasone Butyrate; Clopirac; Cloticasone Propionate; Cormethasone Acetate; Cortodoxone; Deflazacort; Desonide; Desoximetasone; Dexamethasone Dipropionate; Diclofenac Potassium; Diclofenac Sodium; Diflorasone Diacetate; Diflumidone Sodium; Diflunisal ; Difluprednate; Diftalone; Dimethyl Sulfoxide; Drocinonide; Endrysone; Enlimomab ; Enolicam Sodium ; Epirizole ; Etodolac; Etofenamate ; Felbinac; Fenamole; Fenbufen; Fenclofenac; Fenclorac; Fendosal; Fenpipalone; Fentiazac; Flazalone; Fluazacort; Flufenamic Acid; Flumizole; Flunisolide Acetate; Flunixin ; Flunixin Meglumine ; Fluocortin Butyl; Fluorometholone Acetate; Fluquazone; Flurbiprofen ; Fluretofen; Fluticasone Propionate; Furaprofen; Furobufen; Halcinonide; Halobetasol Propionate; Halopredone Acetate; Ibufenac ; Ibuprofen; Ibuprofen Aluminum; Ibuprofen Piconol; Ilonidap; Indomethacin; Indomethacin Sodium; Indoprofen ; Indoxole ; Intrazole; Isoflupredone Acetate; Isoxepac; Isoxicam; Ketoprofen; Lofemizole Hydrochloride ; Lornoxicam ; Loteprednol Etabonate; Meclofenamate Sodium; Meclofenamic Acid; Meclorisone Dibutyrate; Mefenamic Acid ; Mesalamine; Meseclazone; Methylprednisolone Suleptanate; Morniflumate; Nabumetone; Naproxen ; Naproxen Sodium ; Naproxol ; Nimazone; Olsalazine Sodium; Orgotein ; Orpanoxin; Oxaprozin; Oxyphenbutazone; Paranyline Hydrochloride; Pentosan Polysulfate Sodium; Phenbutazone Sodium Glycerate; Pirfenidone ; Piroxicam; Piroxicam Cinnamate; Piroxicam Olamine; Pirprofen; Prednazate; Prifelone; Prednisolone Sodium Phosphate; Prodolic Acid; Proquazone; Proxazole; Proxazole Citrate ; Rimexolone; Romazarit ; Salcolex ; Salnacedin; Salsalate ; Sanguinarium Chloride ; Seclazone ; Sermetacin; Sudoxicam; Sulindac; Suprofen; Talmetacin; Talniflumate ; Talosalate ; Tebufelone ; Tenidap; Tenidap Sodium; Tenoxicam; Tesicam; Tesimide; Tetrydamine ; Tiopinac ; Tixocortol Pivalate; Tolmetin; Tolmetin Sodium; Triclonide; Triflumidate; Zidometacin; Zomepirac Sodium .

Antikeratinizing agent: Doretinel; Linarotene; Pelretin.

Antimalarial : Acedapsone ; Amodiaquine Hydrochloride ; Amquinate; Arteflene; Chloroquine ; Chloroquine Hydrochloride ; Chloroquine Phosphate ; Cycloguanil Pamoate; Enpiroline Phosphate;

Halofantrine Hydrochloride ; Hydroxychloroquine Sulfate ; Mefloquine Hydrochloride; Menoctone; Mirincamycin Hydrochloride ; Primaquine Phosphate; Pyrimethamine; Quinine Sulfate; Tebuquine.

Antimicrobial: Aztreonam; Chlorhexidine Gluconate; Imidurea; Lycetamine; Nibroxane; Pirazmonam Sodium; Propionic Acid ; Pyrithione Sodium; Sanguinarium Chloride ; Tigemonam Dicholine.

Antimigraine: Dolasetron Mesylate ; Naratriptan Hydrochloride; Sergolexole Maleate; Sumatriptan Succinate; Zatosetron Maleate.

Antimitotic: Podofilox.

Antimycotic: Amorolfine.

Antinauseant : Buclizine Hydrochloride ; Cyclizine Lactate; Naboctate Hydrochloride .

Antineoplastic: Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; Adozelesin; Aldesleukin ; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide ; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin ; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine ; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin ; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide ; Cytarabine ; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflornithine Hydrochloride ; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine ; Fludarabine Phosphate; Fluorouracil; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198 ; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofosine;

Isotretinoin; Interferon Alfa-2a ; Interferon Alfa-2b ; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta- I a ; Interferon Gamma- I b; Iproplatin; Irinotecan Hydrochloride ; Lanreotide Acetate; Letrozole; Leuprolide Acetate ; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin ; Prednimustine; Procarbazine Hydrochloride; Puromycin ; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safingol ; Safingol Hydrochloride ; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride.

Other anti-neoplastic compounds include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine;

budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide + estrogen + progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A + myobacterium cell wall sk; mopidamol; multiple drug resistance gene

inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone + pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital

sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer.

Anti-cancer Supplementary Potentiating Agents: Tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitryptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic anti-depressant drugs (e.g., sertraline, trazodone and citalopram); Ca^{++} antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); Calmodulin inhibitors (e.g., prenylamine, trifluoroperazine and clomipramine); Amphotericin B; Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine) and Multiple Drug Resistance reducing agents such as Cremaphor EL. The compounds of the invention also can be administered with cytokines such as granulocyte colony stimulating factor.

Antineutropenic: Filgrastim; Lenograstim; Molgramostim; Regramostim; Sargramostim.

Antiobsessional agent: Fluvoxamine Maleate.

Antiparasitic: Abamectin; Clorsulon; Ivermectin.

Antiparkinsonian: Benztropine Mesylate; Biperiden; Biperiden Hydrochloride; Biperiden Lactate; Carbidopa-Levodopa; Carmantadine; Ciladopa Hydrochloride; Dopamantine; Ethopropazine Hydrochloride; Lazabemide; Levodopa; Lometraline Hydrochloride; Mofegiline Hydrochloride; Naxagolide Hydrochloride; Pareptide Sulfate; Procyclidine Hydrochloride; Quinelorane Hydrochloride; Ropinirole Hydrochloride; Selegiline Hydrochloride; Tolcapone; Trihexyphenidyl Hydrochloride.

Antiperistaltic: Difenoximide Hydrochloride; Difenoxin; Diphenoxylate Hydrochloride; Fluperamide; Lidamidine Hydrochloride; Loperamide Hydrochloride; Malethamer; Nufenoxole; Paregoric.

Antipneumocystic: Atovaquone.

Antiproliferative agent: Piritrexim Isethionate.

Antiprostatic hypertrophy: Sitogluside.

Antiprotozoal: Amodiaquine; Azanidazole; Bamnidazole; Carnidazole; Chlortetracycline Bisulfate ; Chlortetracycline Hydrochloride; Flubendazole; Flunidazole; Halofuginone Hydrobromide; Imidocarb Hydrochloride; Ipronidazole; Metronidazole; Misonidazole; Moxnidazole; Nitarsone; Partricin; Puromycin; Puromycin Hydrochloride; Ronidazole; Sulnidazole; Tinidazole.

Antipruritic: Cyproheptadine Hydrochloride ; Methdilazine; Methdilazine Hydrochloride; Trimeprazine Tartrate.

Antipsoriatic: Acitretin; Anthralin; Azaribine; Calcipotriene; Cycloheximide; Enazadrem Phosphate; Etretinate; Liarozole Fumarate; Lonapalene; Tepoxalin.

Antipsychotic: Acetophenazine Maleate; Alentemol Hydrobromide; Alpertine; Azaperone; Batelapine Maleate; Benperidol; Benzindopyrine Hydrochloride; Brofoxine; Bromperidol; Bromperidol Decanoate; Butaclamol Hydrochloride; Butaperazine; Butaperazine Maleate; Carphenazine Maleate; Carvotroline Hydrochloride; Chlorpromazine; Chlorpromazine Hydrochloride; Chlorprothixene; Cinperene; Cintriamide; Clomacran Phosphate; Clopenthixol; Clopimozide; Clopipazan Mesylate; Cloroperone Hydrochloride; Clothiapine; Clothixamide Maleate; Clozapine; Cyclophenazine Hydrochloride; Droperidol; Etazolate Hydrochloride; Fenimide; Flucindole; Flumezapine; Fluphenazine Decanoate; Fluphenazine Enanthate; Fluphenazine Hydrochloride; Fluspiperone; Fluspirilene; Flutroline; Gevotroline Hydrochloride; Halopemide; Haloperidol; Haloperidol Decanoate; Iloperidone; Imidoline Hydrochloride; Lenperone; Mazapertine Succinate; Mesoridazine; Mesoridazine Besylate; Metiapine; Milenperone; Milipertine; Molindone Hydrochloride; Naranol Hydrochloride; Neflumozide Hydrochloride; Ocaperidone; Olanzapine; Oxiperomide; Penfluridol; Pentiapine Maleate; Perphenazine; Pimozide; Pinoxepin Hydrochloride; Pipamperone; Piperacetazine; Pipotiazine Palmitate; Piquindone Hydrochloride; Prochlorperazine Edisylate; Prochlorperazine Maleate; Promazine Hydrochloride; Remoxipride; Remoxipride Hydrochloride; Rimcazole Hydrochloride; Seperidol Hydrochloride; Sertindole ; Setoperone; Spiperone; Thioridazine ; Thioridazine Hydrochloride; Thiothixene;

Thiothixene Hydrochloride; Tioperidone Hydrochloride; Tiospirone Hydrochloride; Trifluoperazine Hydrochloride; Trifluperidol; Triflupromazine; Triflupromazine Hydrochloride; Ziprasidone Hydrochloride.

Antirheumatic: Auranofin; Aurothioglucose; Bindarit; Lobenzarit Sodium; Phenylbutazone; Pirazolac; Prinomide Tromethamine; Seprilose.

Antischistosomal: Becanthone Hydrochloride; Hycanthone; Lucanthone Hydrochloride; Niridazole; Oxamniquine; Pararosaniline Pamoate; Teroxalene Hydrochloride.

Antiseborrheic: Chloroxine; Piroctone; Piroctone Olamine; Resorcinol Monoacetate.

Antisecretory: Arbaprostil; Deprostil; Fenoctimine Sulfate; Octreotide; Octreotide Acetate; Omeprazole Sodium; Rioprostil; Trimoprostil.

Antispasmodic: Stilonium Iodide; Tizanidine Hydrochloride.

Antithrombotic: Anagrelide Hydrochloride; Bivalirudin ; Dalteparin Sodium ; Danaparoid Sodium; Dazoxiben Hydrochloride; Efegatran Sulfate; Enoxaparin Sodium; Ifetroban; Ifetroban Sodium; Tinzaparin Sodium ; Trifenagrel.

Antitussive: Benzonatate; Butamirate Citrate; Chlophedianol Hydrochloride; Codeine Polistirex; Codoxime; Dextromethorphan; Dextromethorphan Hydrobromide; Dextromethorphan Polistirex; Ethyl Dibunate; Guaiapate; Hydrocodone Bitartrate; Hydrocodone Polistirex; Levopropoxyphene Napsylate; Noscapine; Pemerid Nitrate; Pipazethate; Suxemerid Sulfate.

Anti-ulcerative: Aceglutamide Aluminum; Cadexomer Iodine ; Cetraxate Hydrochloride; Enisoprost; Isotiquimide; Lansoprazole; Lavoltidine Succinate; Misoprostol; Nizatidine; Nolinium Bromide ; Pantoprazole; Pifarnine; Pirenzepine Hydrochloride; Rabeprazole Sodium ; Remiprostol; Roxatidine Acetate Hydrochloride; Sucralfate; Sucrosofate Potassium; Tolimidone.

Anti-urolithic: Cysteamine; Cysteamine Hydrochloride; Tricitrates .

Antiviral: Acemannan; Acyclovir; Acyclovir Sodium; Adefovir; Alovudine; Alvircept Sudotox; Amantadine Hydrochloride; Aranotin; Arildone; Atevirdine Mesylate; Avridine; Cidofovir; Cipamfylline; Cytarabine Hydrochloride; Delavirdine Mesylate; Desciclovir; Didanosine; Disoxaril; Edoxudine; Enviradene; Enviroxime; Famciclovir; Famotine Hydrochloride; Fiacitabine; Fialuridine; Fosarilate; Foscarnet Sodium; Fosfonet Sodium; Ganciclovir; Ganciclovir Sodium; Idoxuridine; Kethoxal; Lamivudine; Lobucavir; Memotine Hydrochloride; Methisazone; Nevirapine; Penciclovir; Pirodavir; Ribavirin; Rimantadine Hydrochloride; Saquinavir Mesylate; Somantadine Hydrochloride; Sorivudine; Statolon; Stavudine; Tilorone Hydrochloride; Trifluridine; Valacyclovir Hydrochloride; Vidarabine; Vidarabine Phosphate; Vidarabine Sodium Phosphate; Viroxime; Zalcitabine; Zidovudine; Zinviroxime.

Appetite suppressant: Dexfenfluramine Hydrochloride; Phendimetrazine Tartrate; Phentermine Hydrochloride.

Benign prostatic hyperplasia therapy agent: Tamsulosin Hydrochloride.

Blood glucose regulators: Human insulin; Glucagon; Tolazamide; Tolbutamide; Chloropropamide; Acetohexamide and Glipizide.

Bone resorption inhibitor: Alendronate Sodium; Etidronate Disodium; Pamidronate Disodium.

Bronchodilator: Albuterol; Albuterol Sulfate; Azanator Maleate; Bamifylline Hydrochloride; Bitolterol Mesylate; Butaprost; Carbuterol Hydrochloride; Clorprenaline Hydrochloride; Colterol Mesylate; Doxaprost; Doxofylline; Dyphylline; Enprofylline; Ephedrine; Ephedrine Hydrochloride; Fenoterol; Fenprinast Hydrochloride; Guaithylline; Hexoprenaline Sulfate ; Hoquizil Hydrochloride; Ipratropium Bromide; Isoetharine; Isoetharine Hydrochloride; Isoetharine Mesylate; Isoproterenol Hydrochloride; Isoproterenol Sulfate; Metaproterenol Polistirex; Metaproterenol Sulfate; Nisbuterol Mesylate; Oxtriphylline; Picumeterol Fumarate; Piquizil Hydrochloride; Pirbuterol Acetate; Pirbuterol Hydrochloride; Procaterol Hydrochloride; Pseudoephedrine Sulfate; Quazodine ; Quinterenol Sulfate; Racepinephrine; Racepinephrine Hydrochloride; Reproterol Hydrochloride; Rimiterol Hydrobromide; Salmeterol; Salmeterol Xinafoate; Soterenol Hydrochloride; Sulfonterol

Hydrochloride; Suloxifen Oxalate; Terbutaline Sulfate; Theophylline; Xanoxate Sodium; Zindotrine; Zinterol Hydrochloride.

Carbonic anhydrase inhibitor: Acetazolamide; Acetazolamide Sodium; Dichlorphenamide; Dorzolamide Hydrochloride; Methazolamide; Sezolamide Hydrochloride.

Cardiac depressant: Acecainide Hydrochloride; Acetylcholine Chloride; Actisomide; Adenosine; Amiodarone; Aprindine; Aprindine Hydrochloride; Artilide Fumarate; Azimilide Dihydrochloride; Bidisomide; Bucainide Maleate; Bucromarone; Butoprozine Hydrochloride ; Capobenate Sodium; Capobenic Acid; Cifenline; Cifenline Succinate; Clofilium Phosphate; Disobutamide; Disopyramide; Disopyramide Phosphate; Dofetilide; Drobuline; Edifolone Acetate; Emilium Tosylate; Encainide Hydrochloride; Flecainide Acetate; Ibutilide Fumarate; Indecainide Hydrochloride; Ipazilide Fumarate; Lorajmine Hydrochloride; Lorcainide Hydrochloride; Meobentine Sulfate; Mexiletine Hydrochloride; Modecainide; Moricizine; Oxiramide; Pirmenol Hydrochloride; Pirolazamide; Pranolium Chloride; Procainamide Hydrochloride; Propafenone Hydrochloride; Pyrinoline; Quindonium Bromide; Quinidine Gluconate; Quinidine Sulfate; Recainam Hydrochloride; Recainam Tosylate; Risotilide Hydrochloride; Ropitoin Hydrochloride; Sematilide Hydrochloride; Suricainide Maleate; Tocainide; Tocainide Hydrochloride; Transcainide.

Cardioprotectant: Dexrazoxane; Draflazine.

Cardiotonic: Actodigin; Amrinone; Bemoradan; Butopamine; Carbazeran; Carsatrin Succinate; Deslanoside; Digitalis; Digitoxin; Digoxin; Dobutamine; Dobutamine Hydrochloride; Dobutamine Lactobionate; Dobutamine Tartrate; Enoximone; Imazodan Hydrochloride; Indolidan; Isomazole Hydrochloride; Levdobutamine Lactobionate; Lixazinone Sulfate; Medorinone; Milrinone; Pelrinone Hydrochloride; Pimobendan; Piroximone; Prinoxodan; Proscillaridin; Quazinone; Tazolol Hydrochloride; Vesnarinone.

Cardiovascular agent: Dopexamine; Dopexamine Hydrochloride.

Choleretic: Dehydrocholic Acid; Fencibutirol; Hymecromone; Piprozolin; Sincalide; Tocamphyl.

Cholinergic: Aceclidine; Bethanechol Chloride; Carbachol; Demecarium Bromide; Dexpanthenol: Echothiophate Iodide; Isoflurophate; Methacholine Chloride; Neostigmine Bromide; Neostigmine Methylsulfate; Physostigmine; Physostigmine Salicylate; Physostigmine Sulfate; Pilocarpine ; Pilocarpine Hydrochloride; Pilocarpine Nitrate; Pyridostigmine Bromide.

Cholinergic agonist: Xanomeline; Xanomeline Tartrate.

Cholinesterase Deactivator: Obidoxime Chloride; Pralidoxime Chloride; Pralidoxime Iodide; Pralidoxime Mesylate.

Coccidiostat: Arprinocid; Narasin ; Semduramicin; Semduramicin Sodium.

Cognition adjuvant: Ergoloid Mesylates; Piracetam; Pramiracetam Hydrochloride; Pramiracetam Sulfate; Tacrine Hydrochloride.

Cognition enhancer: Besipirdine Hydrochloride; Linopirdine; Sibopirdine .

Contrast Media: Barium sulfate (sulfuric acid, barium salt (1:1); synthetic or artificial barytes; artificial heavy spar; blanc fixé; permanent white) - oral suspension; Iopanoic acid (Telepaque) - oral tablet; Ipodate calcium (oragrafin calcium) - oral suspension; Iocetamic acid (Cholebrine) - oral tablet; Diatrizoate sodium (Hypaque sodium) oral and injection; Tyropanoate sodium (Bilopaque) - oral capsule; Erythrosine sodium (Trace) - topical solution and topical tablet; Metyrapone (Metopirone) - oral tablet

Gastric Acid Suppressant: Omeprazole.

Diagnostic aid: Aminohippurate Sodium; Anazolene Sodium; Arclofenin; Arginine ; Bentiromide; Benzylpenicilloyl Polylysine; Butedronate Tetrasodium; Butilfenin; Coccidioidin; Corticorelin Ovine Triflutate ; Corticotropin, Repository ; Corticotropin Zinc Hydroxide; Diatrizoate Meglumine; Diatrizoate Sodium; Diatrizoic Acid; Diphtheria Toxin for Schick Test; Disofenin; Edrophonium Chloride; Ethiodized Oil; Etifenin; Exametazime; Ferristenc; Ferumoxides; Ferumoxsil; Fluorescein; Fluorescein Sodium; Gadobenate Dimeglumine; Gadoteridol; Gadodiamide; Gadopentetate

Dimegiumine; Gadoversetamide; Histoplasmin; Impromidine Hydrochloride; Indigotindisulfonate Sodium; Indocyanine Green ; Iobenguane Sulfate I 123; Iobenzamic Acid; Iocarmate Meglumine; Iocarmic Acid; Iocetamic Acid; Iodamide; Iodamide Megiumine; Iodipamide Meglumine; Iodixanol; Iodoxamate Meglumine; Iodoxamic Acid; Ioglicic Acid; Ioglucol; Ioglucomide; Ioglycamic Acid; Iogulamide; Iohexol; Iomeprol; Iopamidol; Iopanoic Acid; Iopentol; Iophendylate; Iprofenin; Iopronic Acid; Ioprocemic Acid; Iopydol; Iopydone; Iosefamic Acid; Ioseric Acid; Iosulamide Meglumine; Iosumetic Acid; Iotasul; Iotetric Acid; Iothalamate Meglumine; Iothalamate Sodium; Iothalamic Acid; Iotrolan; Iotroxic Acid; Ioversol; Ioxaglate Meglumine; Ioxagiate Sodium; Ioxaglic Acid; Ioxilan; Ioxotrizoic Acid; Ipodate Calcium; Ipodate Sodium; Isosulfan Blue; Leukocyte Typing Serum; Lidofenin; Mebrofenin; Meglumine; Metrizamide; Metrizoate Sodium; Metyrapone; Metyrapone Tartrate; Mumps Skin Test Antigen; Pentetic Acid; Propyliodone; Quinaldine Blue; Schick Test Control; Sermorelin Acetate ; Sodium Iodide I 123; Sprodiamide; Stannous Pyrophosphate; Stannous Sulfur Colloid; Succimer; Teriparatide Acetate; Tetrofosmin; Tolbutamide Sodium; Tuberculin; Tyropanoate Sodium; Xylose.

Diuretic: Ambuphylline ; Ambuside; Amiloride Hydrochloride; Azolimine; Azosemide; Brocrinat; Bumetanide; Chlorothiazide; Chlorthalidone; Clazolimine; Clorexolone; Ethacrynate Sodium; Ethacrynic Acid; Etozolin; Fenquizone; Furosemide; Hydrochlorothiazide; Isosorbide; Mannitol ; Mefruside; Ozolinone; Piretanide; Spiroxasone; Torsemide; Triamterene; Triflocin; Urea.

Dopaminergic agent: Ibopamine.

Ectoparasiticide: Nifluridide; Permethrin.

Emetic: Apomorphine Hydrochloride.

Enzyme inhibitor: Acetohydroxamic Acid; Alrestatin Sodium; Aprotinin; Benazepril Hydrochloride; Benazeprilat; Benurestat; Bromocriptine; Bromocriptine Mesylate; Cilastatin Sodium; Flurofamide; Lergotrile; Lergotrile Mesylate; Levcycloserine; Libenzapril; Pentopril; Pepstatin; Perindopril; Polignate Sodium; Sodium Amylosulfate; Sorbinil; Spirapril Hydrochloride; Spiraprilat; Taleranol; Teprotide; Tolfamide; Zofenopril Calcium.

Estrogen: Chlorotrianisene; Dienestrol; Diethylstilbestrol; Diethylstilbestrol Diphosphate; Equilin; Estradiol; Estradiol Cypionate; Estradiol Enanthate; Estradiol Undecylate; Estradiol Valerate; Estrazinol Hydrobromide; Estriol; Estrofurate; Estrogens, Conjugated; Estrogens, Esterified; Estrone; Estropipate; Ethinyl Estradiol; Fenestrel; Mestranol; Nylestriol; Quinestrol.

Fibrinolytic: Anistreplase; Bisobrin Lactate; Brinolase.

Free oxygen radical scavenger: Pegorgotein.

Gastrointestinal Motility agents: Cisapride (Propulsid); Metoclopramide (Reglan); Hyoscyamine (Levsin).

Glucocorticoid: Amcinonide; Beclomethasone Dipropionate; Betamethasone; Betamethasone Acetate; Betamethasone Benzoate; Betamethasone Dipropionate; Betamethasone Sodium Phosphate; Betamethasone Valerate; Carbenoxolone Sodium; Clocortolone Acetate; Clocortolone Pivalate; Cloprednol; Corticotropin; Corticotropin, Repository; Corticotropin Zinc Hydroxide; Cortisone Acetate; Cortivazol; Descinolone Acetonide; Dexamethasone; Dexamethasone Sodium Phosphate; Diflucortolone; Diflucortolone Pivalate; Flucloronide; Flumethasone; Flumethasone Pivalate; Flunisolide; Fluocinolone Acetonide; Fluocinonide; Fluocortolone; Fluocortolone Caproate; Fluorometholone; Fluperolone Acetate; Fluprednisolone; Fluprednisolone Valerate; Flurandrenolide; Formocortal; Hydrocortisone; Hydrocortisone Acetate; Hydrocortisone Buteprate; Hydrocortisone Butyrate; Hydrocortisone Sodium Phosphate; Hydrocortisone Sodium Succinate; Hydrocortisone Valerate; Medrysone; Methylprednisolone; Methylprednisolone Acetate; Methylprednisolone Sodium Phosphate; Methylprednisolone Sodium Succinate; Nivazol; Paramethasone Acetate; Prednicarbate; Prednisolone; Prednisolone Acetate; Prednisolone Hemisuccinate; Prednisolone Sodium Phosphate; Prednisolone Sodium Succinate; Prednisolone Tebutate; Prednisone; Prednival; Ticabesone Propionate; Tralonide; Triamcinolone; Triamcinolone Acetonide; Triamcinolone Acetonide Sodium; Triamcinolone Diacetate; Triamcinolone Hexacetonide.

Gonad-stimulating principle: Buserelin Acetate; Clomiphene Citrate; Ganirelix Acetate; Gonadorelin Acetate; Gonadorelin Hydrochloride; Gonadotropin, Chorionic; Menotropins.

Hair growth stimulant: Minoxidil .

Hemostatic: Aminocaproic Acid; Oxamarin Hydrochloride; Sulmarin; Thrombin; Tranexamic Acid.

Histamine H2 receptor antagonists: Ranitidine (Zantac); Famotidine (Pepcid); Cimetidine (Tagamet); Nizatidine (Axid).

Hormone: Diethylstilbestrol; Progesterone; 17 hydroxy progesterone; Medroxyprogesterone; Norgestrel; Norethynodrel; Estradiol; Megestrol (Megace); Norethindrone; Levonorgestrel; Ethyndiol; Ethinyl estradiol; Mestranol; Estrone; Equilin; 17 alpha dihydroequilin; equilenin; 17 alpha dihydroequilenin; 17 alpha estradiol; 17 beta estradiol; Leuprolide (lupron); Glucagon; Testolactone; Clomiphene; Han memopausal gonadotropins; Human chorionic gonadotropin; Urofollitropin; Bromocriptine; Gonadorelin; Luteinizing hormone releasing hormone and analogs; Gonadotropins; Danazol; Testosterone; Dehydroepiandrosterone; Androstenedione; Dihydroestosterone; Relaxin; Oxytocin; Vasopressin; Folliculostatin; Follicle regulatory protein; Gonadoctrinins; Oocyte maturation inhibitor; Insulin growth factor; Follicle Stimulating Hormone; Luteinizing hormone; Tamoxifen.; Corticorelin Ovine Triflutate; Cosyntropin; Metogest; Pituitary, Posterior; Seractide Acetate; Somalapor; Somatrem; Somatropin; Somenopor; Somidobove.

Hypocholesterolemic: Lifibrol.

Hypoglycemic: Darglitazone Sodium: Glimepiride.

Hypolipidemic: Azalanstat Dihydrochloride; Colestolone; Surfomer; Xenalipin.

Hypotensive: Viprostol.

HMGCoA reductase inhibitors: Lovastatin (Mevacor); Simvastatin (Zocor); Pravastatin (Pravachol); Fluvasatin (Lescol).

Immunizing agent: Antirabies Serum; Antivenin (Latrodectus mactans); Antivenin (Micrurus Fulvius); Antivenin (Crotalidae) Polyvalent; BCG Vaccine; Botulism Antitoxin; Cholera Vaccine;

Diphtheria Antitoxin; Diphtheria Toxoid; Diphtheria Toxoid Adsorbed; Globulin. Immune; Hepatitis B Immune Globulin; Hepatitis B Virus Vaccine Inactivated; Influenza Virus Vaccine; Measles Virus Vaccine Live; Meningococcal Polysaccharide Vaccine Group A; Meningococcal Polysaccharide Vaccine Group C; Mumps Virus Vaccine Live; Pertussis Immune Globulin; Pertussis Vaccine; Pertussis Vaccine Adsorbed; Plague Vaccine; Poliovirus Vaccine Inactivated; Poliovirus Vaccine Live Oral; Rabies Immune Globulin; Rabies Vaccine; $Rh_0(D)$ Immune Globulin; Rubella Virus Vaccine Live; Smallpox Vaccine; Tetanus Antitoxin; Tetanus Immune Globulin; Tetanus Toxoid; Tetanus Toxoid Adsorbed; Typhoid Vaccine; Yellow Fever vaccine; Vaccinia Immune Globulin; Varicella-Zoster Immune Globulin.

Immunomodulator: Dimepranol Acedoben; Imiquimod; Interferon Beta-1b; Lisofylline; Mycophenolate Mofetil; Prczatide Copper Acetate.

Immunoregulator: Azarole; Fanetizole Mesylate; Frentizole; Oxamisole Hydrochloride; Ristianol Phosphate; Thymopentin; Tilomisole.

Immunostimulant: Loxoribine ; Teceleukin.

Immunosuppressant: Azathioprine; Azathioprine Sodium; Cyclosporine; Daltroban; Gusperimus Trihydrochloride; Prednisolone Sodium Phosphate, Prednisolone; Sirolimus; Tacrolimus.

Impotence therapy adjunct: Delequamine Hydrochloride.

Inhibitor: Acarbose; Atorvastatin Calcium; Benserazide ; Brocresine; Carbidopa; Clavulanate Potassium; Dazmegrel; Docebenone; Epoprostenol; Epoprostenol Sodium; Epristeride; Finasteride; Flurbiprofen Sodium; Furegrelate Sodium; Lufironil; Miglitol; Orlistat; Pimagedine Hydrochloride; Pirmagrel; Ponalrestat; Ridogrel; Sulbactam Benzathine ; Sulbactam Pivoxil ; Sulbactam Sodium ; Suronacrine Maleate; Tazobactam; Tazobactam Sodium; Ticlopidine Hydrochloride; Tirilazad Mesylate; Tolrestat; Velnacrine Maleate; Zifrosilone; Zileuton.

Keratolytic: Alcloxa; Aldioxa; Dibenzothiophene; Etarotene; Isotretinoin; Motretinide; Picotrin Diolamine; Resorcinol Monoacetate ; Salicylic Acid; Sumarotene; Tazarotene; Tetroquinone; Tretinoin.

LHRH agonist: Deslorelin; Goserelin; Histrelin; Lutrelin Acetate; Nafarelin Acetate.

Liver disorder treatment: Malotilate.

Luteolysin: Fenprostalene.

Memory adjuvant: Dimoxamine Hydrochloride; Ribaminol.

Mental performance enhancer: Aniracetam.

Mood regulator: Fengabine.

Mucolytic: Acetylcysteine; Carbocysteine; Domiodol.

Mucosal Protective agents: Misoprostol (Cytotec).

Mydriatic: Berefrine.

Nasal decongestant: Nemazoline Hydrochloride; Pseudoephedrine Polistirex.

Neuroleptic: Duoperone Fumarate; Risperidone.

Neuromuscular blocking agent: Atracurium Besylate; Cisatracurium Besylate; Doxacurium Chloride; Gallamine Triethiodide; Metocurine Iodide; Mivacurium Chloride; Pancuronium Bromide; Pipecuronium Bromide; Rocuronium Bromide; Succinylcholine Chloride; Tubocurarine Chloride; Vecuronium Bromide.

Neuroprotective: Dizocilpine Maleate.

NMDA antagonist: Selfotel.

Non-hormonal sterol derivative: Pregnenolone Succinate.

Oxytocic: Carboprost; Carboprost Methyl; Carboprost Tromethamine; Dinoprost ; Dinoprost Tromethamine ; Dinoprostone ; Ergonovine Maleate; Meteneprost ; Methylergonovine Maleate; Oxytocin; Sparteine Sulfate.

Progestin: Algestone Acetophenide; Amadinone Acetate; Anagestone Acetate; Chlormadinone Acetate; Cingestol; Clogestone Acetate; Clomegestone Acetate; Desogestrel; Dimethisterone; Dydrogesterone; Ethynerone; Ethynodiol Diacetate; Etonogestrel; Flurogestone Acetate; Gestaclone; Gestodene; Gestonorone Caproate; Gestrinone; Haloprogesterone; Hydroxyprogesterone Caproate; Levonorgestrel; Lynestrenol; Medrogestone; Medroxyprogesterone Acetate; Methynodiol Diacetate; Norethindrone; Norethindrone Acetate; Norethynodrel; Norgestimate; Norgestomet; Norgestrel; Oxogestone Phenpropionate; Progesterone; Quingestanol Acetate; Quingestrone; Tigestol.

Prostaglandin: Cloprostenol Sodium; Fluprostenol Sodium; Gemeprost; Prostalene; Sulprostone.

Prostate growth inhibitor: Pentomone.

Prothyrotropin: Protirelin.

Psychotropic: Minaprine.

Radioactive agent: Fibrinogen I 125 ; Fludeoxyglucose F 18 ; Fluorodopa F 18 ; Insulin I 125; Insulin I 131; Iobenguane I 123; Iodipamide Sodium I 131 ; Iodoantipyrine I 131 ; Iodocholesterol I 131 ; Iodohippurate Sodium I 123 ; Iodohippurate Sodium I 125 ; Iodohippurate Sodium I 131 ; Iodopyracet I 125 ; Iodopyracet I 131 ; Iofetamine Hydrochloride I 123 ; Iomethin I 125 ; Iomethin I 131 ; Iothalamate Sodium I 125 ; Iothalamate Sodium I 131 ; Iotyrosine I 131; Liothyronine I 125; Liothyronine I 131; Merisoprol Acetate Hg 197; Merisoprol Acetate Hg 203; Merisoprol Hg 197 ; Selenomethionine Se 75 ; Technetium Tc 99m Antimony Trisulfide Colloid; Technetium Tc 99m Bicisate ; Technetium Tc 99m Disofenin ; Technetium Tc 99m Etidronate ; Technetium Tc 99m

Exametazime ; Technetium Tc 99m Furifosmin ; Technetium Tc 99m Gluceptate ; Technetium Tc 99m Lidofenin ; Technetium Tc 99m Mebrofenin ; Technetium Tc 99m Medronate ; Technetium Tc 99m Medronate Disodium; Technetium Tc 99m Mertiatide ; Technetium Tc 99m Oxidronate ; Technetium Tc 99m Pentetate; Technetium Tc 99m Pentetate Calcium Trisodium; Technetium Tc 99m Sestamibi ; Technetium Tc 99m Siboroxime ; Technetium Tc 99m Succimer ; Technetium Tc 99m Sulfur Colloid ; Technetium Tc 99m Teboroxime ; Technetium Tc 99m Tetrofosmin ; Technetium Tc 99m Tiatide; Thyroxine I 125; Thyroxine I 131; Tolpovidone I 131 ; Triolein I 125; Triolein I 131.

Regulator: Calcifediol; Calcitonin; Calcitriol; Clodronic Acid; Dihydrotachysterol; Etidronic Acid; Oxidronic Acid; Piridronate Sodium; Risedronate Sodium; Secalciferol.

Relaxant: Adiphenine Hydrochloride; Alcuronium Chloride; Aminophylline; Azumolene Sodium; Baclofen; Benzoctamine Hydrochloride; Carisoprodol; Chlorphenesin Carbamate; Chlorzoxazone; Cinflumide; Cinnamedrine; Clodanolene; Cyclobenzaprine Hydrochloride; Dantrolene; Dantrolene Sodium; Fenalamide; Fenyripol Hydrochloride; Fetoxylate Hydrochloride; Flavoxate Hydrochloride; Fletazepam; Flumetramide; Flurazepam Hydrochloride; Hexafluorenium Bromide; Isomylamine Hydrochloride; Lorbamate; Mebeverine Hydrochloride; Mesuprine Hydrochloride ; Metaxalone; Methocarbamol; Methixene Hydrochloride; Nafomine Malate; Nelezaprine Maleate; Papaverine Hydrochloride; Pipoxolan Hydrochloride; Quinctolate; Ritodrine; Ritodrine Hydrochloride; Rolodine; Theophylline Sodium Glycinate; Thiphenamil Hydrochloride; Xilobam.

Repartitioning agent: Cimaterol.

Scabicide: Amitraz; Crotamiton.

Sclerosing agent: Ethanolamine Oleate; Morrhuate Sodium; Tribenoside.

Sedative: Propiomazine.

Sedative-hypnotic: Allobarbital; Alonimid; Alprazolam; Amobarbital Sodium; Bentazepam; Brotizolam; Butabarbital; Butabarbital Sodium; Butalbital; Capuride; Carbocloral; Chloral Betaine;

Chloral Hydrate; Chlordiazepoxide Hydrochloride; Cloperidone Hydrochloride; Clorethate; Cyprazepam; Dexclamol Hydrochloride; Diazepam; Dichloralphenazone; Estazolam; Ethchlorvynol; Etomidate; Fenobam; Flunitrazepam; Fosazepam; Glutethimide; Halazepam; Lormetazepam; Mecloqualone; Meprobamate; Methaqualone; Midaflur; Paraldehyde; Pentobarbital; Pentobarbital Sodium; Perlapine; Prazepam; Quazepam; Reclazepam; Roletamide; Secobarbital; Secobarbital Sodium; Suproclone; Thalidomide; Tracazolate; Trepipam Maleate; Triazolam; Tricetamide; Triclofos Sodium; Trimetozine; Uldazepam; Zaleplon; Zolazepam Hydrochloride; Zolpidem Tartrate.

Selective adenosine Al antagonist: Apaxifylline.

Serotonin antagonist: Altanserin Tartrate; Amesergide; Ketanserin; Ritanserin.

Serotonin inhibitor: Cinanserin Hydrochloride; Fenclonine; Fonazine Mesylate: Xylamidine Tosylate.

Serotonin receptor antagonist: Tropanserin Hydrochloride.

Steroid: Dexamethasone Acefurate; Mometasone Furoate.

Stimulant: Amfonelic Acid; Amphetamine Sulfate; Ampyzine Sulfate; Arbutamine Hydrochloride; Azabon; Caffeine; Ceruletide; Ceruletide Diethylamine; Cisapride; Dazopride Fumarate; Dextroamphetamine; Dextroamphetamine Sulfate; Difluanine Hydrochloride; Dimefline Hydrochloride; Doxapram Hydrochloride; Etryptamine Acetate; Ethamivan; Fenethylline Hydrochloride; Flubanilate Hydrochloride; Flurothyl; Histamine Phosphate; Indriline Hydrochloride; Mefexamide; Methamphetamine Hydrochloride; Methylphenidate Hydrochloride; Pemoline; Pyrovalerone Hydrochloride; Xamoterol; Xamoterol Fumarate.

Suppressant: Amflutizole; Colchicine; Tazofelone.

Symptomatic multiple sclerosis: Fampridine.

Synergist: Proadifen Hydrochloride.

Thyroid hormone: Levothyroxine Sodium; Liothyronine Sodium; Liotrix.

Thyroid inhibitor: Methimazole; Propylthiouracil.

Thyromimetic: Thyromedan Hydrochloride.

Tranquilizer: Bromazepam; Buspirone Hydrochloride; Chlordiazepoxide; Clazolam; Clobazam; Clorazepate Dipotassium; Clorazepate Monopotassium; Demoxepam; Dexmedetomidine; Enciprazine Hydrochloride; Gepirone Hydrochloride; Hydroxyphenamate; Hydroxyzine Hydrochloride; Hydroxyzine Pamoate; Ketazolam; Lorazepam; Lorzafone; Loxapine; Loxapine Succinate; Medazepam Hydrochloride; Nabilone; Nisobamate ; Oxazepam; Pentabamate; Pirenperone; Ripazepam; Rolipram; Sulazepam; Taciamine Hydrochloride; Temazepam; Triflubazam; Tybamate; Valnoctamide.

Amyotrophic lateral sclerosis agents: Riluzole.

Cerebral ischemia agents: Dextrorphan Hydrochloride.

Paget's disease agents: Tiludronate Disodium.

Unstable angina agents: Tirofiban Hydrochloride.

Uricosuric: Benzbromarone; Irtemazole; Probenecid; Sulfinpyrazone.

Vasoconstrictor : Angiotensin Amide; Felypressin; Methysergide; Methysergide Maleate.

Vasodilator: Alprostadil; Azaclorzine Hydrochloride; Bamethan Sulfate; Bepridil Hydrochloride; Buterizine; Cetiedil Citrate; Chromonar Hydrochloride; Clonitrate; Diltiazem Hydrochloride; Dipyridamole; Droprenilamine; Erythrityl Tetranitrate; Felodipine; Flunarizine Hydrochloride; Fostedil; Hexobendine; Inositol Niacinate; Iproxamine Hydrochloride; Isosorbide Dinitrate;

Isosorbide Mononitrate; Isoxsuprine Hydrochloride; Lidoflazine; Mefenidil; Mefenidil Fumarate; Mibefradil Dihydrochloride; Mioflazine Hydrochloride; Mixidine; Nafronyl Oxalate; Nicardipine Hydrochloride; Nicergoline; Nicorandil; Nicotinyl Alcohol; Nifedipine; Nimodipine; Nisoldipine; Oxfenicine; Oxprenolol Hydrochloride; Pentaerythritol Tetranitrate; Pentoxifylline; Pentrinitrol; Perhexiline Maleate; Pindolol; Pirsidomine; Prenylamine; Propatyl Nitrate; Suloctidil; Terodiline Hydrochloride; Tipropidil Hydrochloride; Tolazoline Hydrochloride; Xanthinol Niacinate.

Vulnerary: Allantoin.

Wound healing agent: Ersofermin.

Xanthine oxidase inhibitor: Allopurinol; Oxypurinol

Other pharmaceutical agents include: 1-decpyrrolidinone; 1-dodecpyrrolidinone; 16-alpha fluoroestradiol; 16-epiestriol; 16alpha-gitoxin; 17alpha estradiol; 17beta estradiol; 1alpha-hydroxyvitamin D2; 2'-nor-cGMP; 20-epi-1,25 dihydroxyvitamin D3; 22-oxacalcitriol; 2CVV; 3-isobutyl GABA; 6-FUDCA; 7-methoxytacrine; abamectin; abanoquil; abecarnil; abiraterone; acadesine; acamprosate; acarbose; aceclofenac; acemannan; acetomepregenol; acetyl-L-carnitine; acetylcysteine, N-; acetylmethadol; acifran; acipimox; acitemate; acitretin; aclarubicin; aclatonium; napadisilate; aconiazide; acrivastinet; adafenoxate; adapalene; adatanserin; adecypenol; adefovir dipivoxil; adelmidrol; ademetionine; adinazolam; adiposin; adozelesin; adrafinil; alacepril; aladapcin; alaptide; albendazole; albolabrin; aldecalmycin; aldesleukin; alendronic acid; alentemol; alfacalcidol; alfuzosin; alglucerase; alinastine; alosetron; alpha idosone; alprostadil; altretamine; altromycin B; ambamustine; amelometasone; amesergide; amezinium metilsulfate; amfebutamone; amidox; amifloxacin; amifostine; amiodarone; amisulpride; amlexanox; amlodipine; amlodipine; ampiroxicam; amrinone; amrubicin; amsacrine; amylin; amythiamicin; anagrelide; anakinra; ananain; anaritide; anastrozole; andrographolide; anordrin; apadoline; apafant; apaxifylline; aphidicolin glycinate; apraclonidine; aprosulate sodium; aptiganel; apurinic acid; aranidipine; arbekacin; arbidol; arbutamine; ardeparin sodium; arecatannin B1; argatroban; aripiprazol; arotinolol; asimadoline; aspalatone; asperfuran; aspoxicillin; astemizole; asulacrine; atamestane; atenolol, S-; atevirdine; atosiban; atovaquone; atpenin B; atrimustine; atrinositol; aureobasidin A; azadirachtine; azasetron; azatyrosine; azelaic acid; azelastine; azelnidipine;

azimilide; azithromycin; azosemide; aztreonam; baccatin III; bacoside A; bacoside B; bactobolamine; balazipone; balhimycin;. balofloxacin; balsalazide; bambuterol; baohuoside 1; barnidipine; basifungin; batebulast; batimastat; beauvericin; becaplermin; becliconazole; befloxatone; belfosdil; bellenamine; benflumetol; benidipine; benzisoxazole; benzochlorins; benzoidazoxan; benzoylstaurosporine; benztropine; bepridil; beractant; beraprost; berlafenone; bertosamil; besipirdine; beta-alethine; betaclamycin B; betamipron; betaxolol; betulinic acid; bevantolol; bicalutamide; bifemelane; bimakalim; bimithil; binospirone; bioxalomycin alpha2; biriperone; bis-benzimidazole A; bis-benzimidazole B; bisantrene; bisaramil; bisaziridinylspermine; bisnafide; bisoprolol; bistramide D; bistramide K; bistratene A; boldine; bopindolol; brefeldin; breflate; brimonidine; bromfenac; bromperidol; bropirimine; bucindolol; budesonide; budipine; budotitane; bunaprolast; bunazosin; butenafine; buthionine sulfoximine; butixocort propionate; cadexomer iodine; calanolide A; calcipotriol; calphostin C; camonagrel; candesartan; candesartan cilexetil; candoxatril; candoxatrilat; capecitabine; capromab; capsaicin; captopril; carbazomycin C; carbetocin; carbovir; carboxamide-amino-triazole; carboxyamidotriazole; carboxymethylated beta-1,3-glucan; carperitide; carteolol; carumonam; carvedilol; carvotroline; carzelesin; castanospermine; cebaracetam; cecropin B; cefcapene pivoxil; cefdaloxime pentexil tosilate; cefdinir; cefditoren pivoxil; cefepime; cefetamet; cefetamet pivoxil; cefixime; ceflupranam; cefmetazole; cefminox; cefodizime; cefoselis; cefotetan; cefotiam; cefotiam hexetil; cefozopran; cefpimizole; cefpiramide; cefpirome; cefpodoxime proxetil; cefprozil; cefsulodin; cefteram; ceftibuten; ceftriaxone; cefuroxime axetil; celastrol; celikalim; celiprolol; cepacidine A; cericlamine; cerivastatin; ceronapril; certoparin sodium; cetiedil; cetirizine; chloroorienticin A; chloroorienticin B; chloroquinoxaline sulfonamide; cibenzoline; cicaprost; ciclesonide; cicletanine; cicloprolol; cidofovir; cilansetron; cilazapril; cilnidipine; cilobradine; cilostazol; cimetropium bromide; cinitapride; cinolazepam; cioteronel; ciprofibrate; ciprofloxacin; ciprostene; cis-porphyrin; cisapride; cisatracurium besilate; cistinexine; citalopram; citicoline; citreamicin alpha; cladribine; clarithromycin; clausenamide; clebopride; clinafloxacin; clobazam; clobetasone butyrate; clodronic acid; clomethiazole; clopidogrel; clotrimazole; colestimide; colfosceril palmitate; collismycin A; collismycin B; combretastatin A4; complestatin; conagenin; contignasterol; contortrostatin; cosalane; costatolide; cotinine; coumermycin A1; cucumariosid; curacin A; curdlan sulfate; curiosin; cyclazosin; cyclic HPMPC; cyclobenzaprine; cyclobut A; cyclobut G; cyclocapron; cycloplatam; cyclosin; cyclothialidine; cyclothiazomycin; cypemycin; cyproterone; cytarabine ocfosfate; cytochalasin B; dacliximab; dactimicin; daidzein; daidzin; dalfopristin; dalteparin sodium;

danaparoid; daphnodorin A; dapiprazole; dapitant; darifenacin; darlucin A; darsidomine; ddUTP; decitabine; deferiprone; deflazacort; dehydrodidemnin B; dehydroepiandrosterone; delapril; delequamine; delfaprazine; delmopinol; delphinidin; deoxypyridinoline; deprodone; depsidomycin; deramciclane; dermatan sulfate; desflurane; desirudin; deslorelin; desmopressin; desogestrel; desoxoamiodarone; detajmium bitartrate; dexifosfamide; dexketoprofen; dexloxiglumide; dexmedetomidine; dexpemedolac; dexrazoxane; dexsotalol; dextrin 2-sulphate; dexverapamil; dezinamide; dezocine; diaziquone; diclofenac digolil; diclofenac potassium; dicranin; didemnin B; didox; dienogest; diethylhomospermine; diethylnorspermine; dihydrexidine; dihydro-5-azacytidine; dimethyl prostaglandin A1; dimethylhomospermine; dimiracetam; dioxamycin; diphencyprone; diphenyl spiromustine; diprafenone; dipropylnorspermine; dirithromycin; discodermolide; disulfiram; ditekiren; docarpamine; docosanol, 1-; dofetilide; dolasetron; domitroban; dopexamine; dorzolamide; dosmalfate; dotarizine; doxacurium chloride; doxazosin; doxifluridine; doxofylline; draculin; draflazine; droloxifene; dronabinol; drosperidone; drotaverine acephyllinate; droxicam; ebiratide; ebrotidine; ebselen; ecabapide; ecabet; ecadotril; ecdisteron; echicetin; echistatin; ecomustine; ecteinascidin 722; ecteinascidin 729; ecteinascidin 743; edaravone; edelfosine; edobacomab; edrecolomab; efegatran; eflornithine; efonidipine; egualen; elcatonin; eletriptan; elgodipine; eliprodil; eltenac; emakalim; emedastine; emiglitate; emitefur; emoctakin; enadoline hydrochloride; enalapril; enazadrem; englitazone; enlimomab; enoxacin; enoxaparin sodium; enoximone; entacapone; enterostatin; epoprostenol; epoxymexrenone; epristeride; eprosartan; eptastigmine; erdosteine; ersentilide; ersofermin; erythritol; esuprone; etanidazole; etanterol; ethacizin; ethinylestradiol; etizolam; etodolac; etoposide phosphate; etrabamine; everninomicin; examorelin; exemestane; fadrozole; faeriefungin; famciclovir; fampridine; fantofarone; faropenem; fasidotril; fasudil; fazarabine; fedotozine; felbamate; fenofibrate; fenoldopam; fenretinide; fenspiride; fenticonazole; fepradinol; ferpifosate sodium; ferristene; ferrixan; ferumoxsil; flavopiridol; flecainide; flerobuterol; fleroxacin; flesinoxan; flezelastine; flobufen; flomoxef; florfenicol; florifenine; flosatidil; fluasterone; fluconazole; fludarabine; flumazenil; flumecinol; flumequine; flunarizine; fluocalcitriol; fluorodaunorunicin hydrochloride; fluoxetine, R-; fluoxetine, S-; fluparoxan; flupirtine; flurbiprofen axetil; flurithromycin; fluticasone propionate; flutrimazole; fluvastatin; fluvoxamine; forasartan; forfenimex; formestane; formoterol; formoterol, R,R-; fosfomycin; trometamol; fosinopril; fosphenytoin; fostriecin; fotemustine; gabapentin; gadobenic acid; gadobutrol; gadodiamide; gadodiamide-EOB-DTPA; gadolinium texaphyrin; gadoteric acid; gadoteridol; gadoversetamide; galantamine; galdansetron; gallopamil; galocitabine; gamolenic acid;

ganirelix; gepirone; gestrinone; girisopam; glaspimod; glaucocalyxin A; glutapyrone; glycopine; glycopril; granisetron; grepafloxacin; halichondrin B; halofantrine; halomon; halopredone; hatomamicin; hatomarubigin A; hatomarubigin B; hatomarubigin C; hatomarubigin D; ibogaine; ibopamine; ibudilast; illimaquinone; ilmofosine; ilomastat; iloperidone; iloprost; imidapril; imidazenil; indinavir; indolidan; indometacin farnesil; indometacin; tropine ester; indoramin; inocoterone; inogatran; inolimomab; interferon alfa; interferon alfa-2a; interferon alfa-2b; interferon alfa-N1; interferon alfa-n3; interferon beta; interferon beta-1al; interferon beta-1b; interferon gamma-1a; interferon gamma-1b; interferon omega; interferon, consensus; interleukin-1; interleukin-1 alpha; interleukin-1 beta; interleukin-10; interleukin-11; interleukin-12; interleukin-12; interleukin-15; interleukin-2; interleukin-3; interleukin-4; interleukin-5; interleukin-7; interleukin-8; iobenguane; iobitridol; iodoamiloride; iododoxorubicin; iofratol; iomeprol; iopentol; iopromide; iopyrol; iotriside; ioversol; ioxilan; ipazilide; IpdR; ipenoxazone; ipidacrine; ipomeanol, 4-; ipriflavone; ipsapirone; irbesartan; irinotecan; irloxacin; irsogladine; irtemazole; isalsteine; isbogrel; isepamicin; isobengazole; isofloxythepin; isohomohalicondrin B; isopropyl unoprostone; isradipine; itameline; itasetron; itopride; itraconazole; ketoprofen, R-; ketoprofen, S-; ketorolac; lacidipine; lactitol; lactivicin; laennec; lafutidine; lamellarin-N triacetate; lamifiban; lamivudine; lamotrigine; lanoconazole; lanperisone; lanreotide; lansoprazole; latanoprost; lateritin; laurocapram; lazabemide; lemefloxacin; lemildipine; leminoprazole; lenercept; lenograstim; lentinan sulfate; leptin; leptolstatin; lercanidipine; lerisetron; lesopitron; letrazuril; letrozole; leucomyzin; leuprorelin; levcromakalim; levetiracetam; levobetaxolol; levobunolol; levobupivacaine; levocabastine; levocarnitine; levodropropizine; levofloxacin; levomoprolol; levonorgestrel; levormeloxifene; levosimendan; levosulpiride; linotroban; linsidomine; lintitript; lintopride; liothyronine sodium; lirexapride; lisinopril; lobaplatin; lobucavir; lodoxamide; lombricine; lomefloxacin; lomerizine; lometrexol; lonazolac; lonidamine; loracarbef; loratadine; lorglumide; lornoxicam; losartan; losigamone; losoxantrone; loteprednol; loviride; loxoribine; lubeluzole; lurtotecan; luteinizing hormone; lutetium; luzindole; lydicamycin; lysofylline; lysostaphin; magainin 2 amide; magnolol; mallotochromene; mallotojaponin; malotilate; mangafodipir; manidipine; maniwamycin A; mannostatin A; manumycin E; manumycin F; mapinastine; marimastat; Martek 8708; Martek 92211; masoprocol; maspin; massetolide; meterelin; methoxatone; methylhistamine, R-alpha; methylinosine monophosphate; methylprednisolone aceponate; methylprednisolone suleptanate; metipamide; metoclopramide; metoprolol, S-; metrifonate; mibefradil; michellamine B; microcolin A; midodrine; mifepristone; miglitol; milacemide; milameline; mildronate; milnacipran; milrinone;

miltefosine; minaprine; miokamycin; mipragoside; mirfentanil; mirimostim; mirtazapine; misoprostol; mitoguazone; mitolactol; mitonafide; mitoxantrone; mivacurium chloride; mivazerol; mixanpril; mizolastine; mizoribine; moclobemide; modafinil; moexipril; mofarotene; mofezolac; molgramostim; mometasone; montirelin; mopidamol; moracizine; mosapramine; mosapride; motilide; moxiraprine; moxonidine; nadifloxacin; nadroparin calcium; nafadotride; nafamostat; nafarelin; naftopidil; naglivan; nagrestip; nalmefene; naphterpin; napsagatran; naratriptan; nartograstim; nasaruplase; nateplase; niperotidine; niravoline; nisamycin; nisin; nisoldipine; nitazoxanide; nitecapone; nitrendipine; nitrendipine, S-; nitrofurantoin monohydrate; nitrullyn; nizatidine; ofloxacin; okicenone; olanzapine; olopatadine; olprinone; olsalazine; omeprazole; onapristone; ondansetron; ondansetron, R-; ontazolast; oracin; otenzepad; oxaliplatin; oxamisole; oxandrolone; oxaprozin; oxaunomycin; oxcarbazepine; oxiconazole; oxiracetam; oxodipine; ozagrel; palauamine; palinavir; palmitoylrhizoxin; pamaqueside; pamicogrel; pamidronic acid; panamesine; panaxytriol; panipenem; panipenum; pannorin; panomifene; pantethine; pantoprazole; parabactin; parnaparin sodium; paroxetine; parthenolide; pazelliptine; pazufloxacin; pefloxacin; pegaspargase; peldesine; pemedolac; pemirolast; penciclovir; pentafuside; pentamidine; pentamorphone; pentigetide; pentosan; pentostatin; pentrozole; perflubron; perfosfamide; pergolide; perindoprilat; perospirone; phenaridine; phenazinomycin; phenserine; phensuccinal; phentolamine mesilate; phenylacetate; phenylalanyl ketoconazole; picenadol; picibanil; picroliv; picumeterol; pidotimod; pilocarpine hydrochloride; pilsicainide; pimagedine; pimilprost; pimobendan; pinacidil; pinocebrin; pioglitazone; pipecuronium bromide; pirarubicin; piretanide; pirfenidone; piritrexim; pirlindole; pirmagrel; pirmenol; pirodavir; pirodomast; piroxicam cinnamate; propagermanium; propentofylline; propionylcarnitine, L-; propiram; propiram + paracetamol; propiverine; propyl bis-acridone; prostaglandin J2; prostratin; protegrin; protosufloxacin; prulifloxacin; pyrazoloacridine; quazepam; quetiapine; quiflapon; quinagolide; quinapril; quinfamide; quinupristin; raloxifene; raltitrexed; ramatroban; ramipril; ramosetron; ranelic acid; ranitidine bismuth citrate; ranolazine; recainam; regavirumab; relaxin; repirinast; resinferatoxin; reticulon; reviparin sodium; revizinone; ricasetron; ridogrel; rifabutin; rifapentine; rifaximin; rilopirox; riluzole; rimantadine; rimexolone; rimoprogin; riodipine; ripisartan; risedronic acid; rispenzepine; risperidone; ritanserin; ritipenem; ritipenem acoxil; ritolukast; ritonavir; rizatriptan benzoate; rohitukine; rokitamycin; ropinirole; ropivacaine; roquinimex; roxatidine; roxindole; roxithromycin; rubiginone B1; ruboxyl; rufloxacin; rupatidine; ruzadolane; safingol; safironil; saintopin; salbutamol, R-; salmeterol; salmeterol, R-salnacedin; sameridine; sampatrilat; sanfetrinem; saprisartan; sapropterin; saquinavir; SarCNU; sarcophytol A

sargramostim; sarpogrelate; saruplase; saterinone; satigrel; satumomab pendetide; selegiline; selenium thiosemicarbazone; sematilide; semduramicin; semotiadil; semustine; sermorelin; sertaconazole; sertindole; sertraline; setiptiline; sevirumab; sevoflurane; sezolamide; silipide; silteplase; simendan; simvastatin; sinitrodil; sinnabidol; sipatrigine; sirolimus; sizofiran; somatomedin B; somatomedin C; somatrem; somatropin; sonermin; sotalol; staurosporine; stavudine; stepronin; stipiamide; stiripentol; stobadine; succibun; sucralfate; sulfasalazine; sulfinosine; sulfoxamine; sulopenem; sultamicillin; sultopride; sulukast; sumatriptan; symakalim; tandospirone; tapgen; taprostene; tasosartan; tazanolast; tazarotene; teicoplanin; telenzepine; tellurapyrylium; telmesteine; telmisartan; temocapril; temoporfin; temozolomide; tenidap; teniposide; tenosal; tenoxicam; tepirindole; tepoxalin; terazosin; terbinafine; terfenadine; terflavoxate; terguride; terlakiren; terlipressin; terodiline; tertatolol; testosterone buciclate; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thiofedrine; thiomarinol; thioperamide; thyroid stimulating hormone; tiagabine; tianeptine; tiapafant; tibolone; ticlopidine; tienoxolol; tilisolol; tilnoprofen arbamel; tiludronic acid; tinzaparin sodium; tiotropium bromide; tipredane; tiqueside; tirandalydigin; tirapazamine; tirilazad; tirofiban; tiropramide; topsentin; torasemide; toremifene; tosufloxacin; trafermin; trandolapril; traxanox; tretinoin; tretinoin tocoferil; triacetyluridine; tricaprilin; trichohyalin; trichosanthin, alpha; triciribine; trientine; triflavin; trimegestone; triptorelin; troglitazone; trombodipine; tropisetron; trospectomycin; trovafloxacin; trovirdine; tucaresol; tulobuterol; tylogenin; urapidil; uridine triphosphate; valaciclovir; valproate magnesium; valproate semisodium; valsartan; vamicamide; vanadeine; vaninolol; vapreotide; variolin B; velaresol; venlafaxine; veramine; verapamil, (S); verdins; veroxan; verteporfin; vesnarinone; vexibinol; vigabatrin; vinburnine citrate; vinburnine resinate; vinconate; vinorelbine; vinpocetine; vinpocetine citrate; vintoperol; vinxaltine; voriconazole; vorozole; voxergolide; xemilofiban; ximoprofen; yangambin; zabicipril; zacopride; zacopride, R-; zafirlukast; zalcitabine; zaleplon; zalospirone; zaltoprofen; zanamivir; zankiren; zanoterone; zatebradine; zatosetron; zenarestat; zeniplatin; zifrosilone; zilascorb; zileuton; zinostatin stimalamer; ziprasidone; zoledronic acid; zolmitriptan; zolpidem; zonisamide; zopiclone; zopiclone, S-; zopolrestat; zotepine.

Also included are commonly used geriatric drugs, such as furosemide; digoxin; potassium chloride; divalproex; trazodone-HCl, ranitidine; phenytoin sodium, sertraline-HCl, risperidone, omeprazole; folic acid; haloperidol; nizatidine; carbamazepine; metoprotol tartrate; lisinopril; warfarin; cisapride; hydrochlorothiazide; nitroglycerin; methyl-dopa; carbi-dopa/levodopa; prazosin;

oral hypoglyceremics; amantadine-HCl; hyoscyamine sulfate; fluoxetine; nifidipine: diltiazeim; phenotoxifyline; ketoprofen; aspirin; piroxicam; indomethacin; ibuprofen; isotretinoin; triamtevene.

Particularly important agents are:amantadine hydrochloride, hyoscyamine sulfate, fluoxetine and trazodone hydrochloride for neurological disorders; nifidipine; diltiazem, phenotoxifyline for cardiovascular disease; ketoprofen, aspirin, piroxicam, indomethacin, ibuprofen for arthritis; omeprazole for ulcers, isotretinoin for cancer oxazepain, lorazepam, piroxicam, loperamide, bromopheniramine, phenylpropanolanime, loratadine, famotidine, ordansetron, enalapril, captopril, phloroglucinol, nicergoline, acetaminophen, metapimazine, dihydroergotamine, fexofenadine-HCl and albuterol.

Additional agents can be found in "Oral Solid Dosage Forms That Should Not Be Crushed: 1996 Revision" by John F. Mitchell, Pharm D published in Hospital Pharmacy, volume 31, pp.27-37, 1996.

The agent delivered by the flakes of the invention also may be a vitamin, mineral, essential nutrient or herbal agent.

Vitamins include: Fat Soluble Vitamins: Vitamin D, Vitamin E, Vitamin K; Water-Soluble Vitamins, Ascorbic Acid (vitamin C), Thiamine (vitamin B1), Riboflavin (vitamin B2), Niacin (vitamin B3), Pyridoxine (vitamin B6), Cyanocobalamin (vitamin B12), Folic acid, Pantothenic Acid (in b complex family); Other Vitamins: Biotin (vitamin H), Laetrile (amygdalin, vitamin B17), Pangamic acid (vitamin B15), Taurine (aminoethanesulfonate).

Minerals (including race elements): Minerals: Calcium, Iron, Magnesium, Phosphorus; Trace Elements: Chromium, Cobalt, Copper, Flourine, Iodine, Manganese, Molybdenum, Nickel, Selenium, Silicon, Tin, Vanadium, Zinc.

Essential nutrients: the essential immuno acids, including argenine, histadine, isoleucine, leucine, lycine, mathyonine, phenylalanine, threonine, tryptofan and baline; Essential fatty acids: inositol; choline, and the vitamins thiamine, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, B12, and folic acid.

The agent also can be an herbal active agent. An herbal active agent as used herein is ground herbs or herb extracts which are commonly used to treat medical conditions or as nutritional supplements. Common herbal and phytochemical products include:

<u>Products for Digestive System Disorders</u>

Chamomile (*Matricaria recutita L.*); Ginger (*Zingiber officinale* Rosc.); Licorice (*Glycyrrhiza glabra* L., *Glycyrrhiza uralensis* Fisch.); Milk Thistle (*Silybum marianum* L.); Peppermint (*Mentha x piperita* L.);

Plantago Seed, Psyllium Seed (*Plantago arenaria* Waldst., *Plantago arencria* Kit., *Plantago ovata):* Senna (*Cassia acutifolia* Del. *Cassia angustifolia* Vahl., *Senna alexandrina* Mill.)

Products for Kidney, Urinary Tract, and Prostate Disorders

Beaberry (*Arctostaphylos uva-vrsi* (L., Spreng- (Ericacaeae)); Cranberry (*Vaccinium macrocarpon* Ait.); Goldenrod (*Solidago virgaurea* L., *Solidago serotina* Ait., *Solidago canadensis* L.); Saw Palmetto (*Serenoa repens* (Batr.)

Products for Performance and Endurance Enhancers

Echinacea (*Echinacea purpurea* (L.) Moench., *Echinacea angustifolia* DC, *Echinacea pallida* (Nutt.) Nutt.)
Eleuthero (*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim)
Ginseng (*Panex ginseng* C.A. Meyer, *panax quinquefolius* L.)

Products for Nervous System Disorders

Feverfew (*Tanacetum parthenium* L.); St. John's Wort (*Hypericum perforatum* L.); Valerian (*Valeriana officinalis* L.); Willow Bark (*Salix alba* L., *Salix fragilis* L, *Salix daphnoides* Villars, *Salix pentandra* L.)

Products for Metabolic and Endocrine Disorders

Black Cohosh (*Cimicifuga racemosa* (L.) (Nutt.); Black Currant Seed Oil (*Ribes nigrum* L.); Borage Seed Oil (*Borago officinalis* L.,); Chaste Tree Berry (*Vitex agnus-castus* L.); Evening Primrose Oil (*Oenothera biennis L.)*

Products for Respiratory Tract Disorders

Ephedra (*Ephedra sinica* Stapf., *Ephedra intermedia* Schrank., *Ephedra equisetina* Bunge.); Horehound (*Marrubium vulgare* L.); Slippery Elm (*Ulmus rubra* Muhl.)

Products for Cardiovascular System Disorders

Garlic (*Allium sativum* L.); Ginkgo (*Ginkgo biloba* L.); Grapeseed (*vitis vinifera* L.); Hawthorn (*Crataegus laevigata* (Pior) DC; Pinebark (*Pinus maritima* Lam.), pycnogenol

Products for Disorders of the Skin, Mucous Membranes and Gingiva

Aloe Vera Gel (*Alo vera* (L.) N.L. Burm.); Goldenseal (*Hydrastis canadensis* L.); Melissa (*Melissa officinalis* L.), Lemon Balm; Tea Tree Oil (*Melaleuca alternifolia* (Maiden & Betche) Cheel); Witch Hazel (*Hamamelis virginiana* L., *Hamamelis vernalis* Sarg.)

Important Combinations are (1) diagnostic agent flakes for GI contrast composed of barium salt, a laxative, and/or an antiflatulant/lubricant, and/or a coating material, and/or an excipient; (2) an osteoporosis flake composed of: calcium, vitamin D (or its analogs), magnesium, and, optionally, boron; (3) a cardiology flake composed of: folic acid, nicitimic acid, vitamin E, lethitan, and/or an excipient, and/or a coating material.

The agent may be a sunscreen agent. Examples of sunscreen agents include: p-aminobenzoate analogs such as 2-ethylhexyl-4-dimethylaminobenzoate (Padimate O); p-methoxy-2-ethyl-hexyl-cinnamate (Parsol 1789); oxybenzone (benzophenone-3); ethylhexylsalicylate; diphenylacrylate polyisobutylene; alkyl-β,β-diphenylacrylate and α-cyano-β,β-diphenylacrylate;1-(4-aminophenyl)-2-morpholinylethanone;(1-(4-methoxylphenyl)-3-(4-tert-butyl-phenyl)-propan-1-3-dione; methyl anthranilate; octocrylene; Tretinoin α-hydroxyacid; diphenylacrylate polyisobutylene; 1-(4-aminophenyl)-2-morpholinylethanone; diphenylacrylate polyisobutylene; digalloyl trioleate; glyceryl p- aminobenzoate; 4-(omega - dialkylaminoalkoxy)phenylmethylene)-1,3,3-trimethyl-2-oxabicyclo(2.2.2)octan-6-ones; 5-(arylmethylene)-1,3,3-trimethyl-2-oxabicyclo(2.2.2)octan-6-ones; melanin.

The agent also can be insect repellants. A widely used insect repellant is N-N-diethyl-3-methylbenzamide.

The agent also may be cultured cells, lyophillized and captured within the matrix of the flake. Such cells can be recombinant cells engineered to produce desirable therapeutic products.

Imaging agents are agents capable of imaging a desired site, e.g. tumor, in vivo. Examples of imaging agents include substances having a label which is detectable in vivo, e.g. antibodies attached to fluorescent labels. The term antibody includes whole antibodies or fragments thereof.

Neurotransmitters are substances which are released from a neuron on excitation and travel to either inhibit or excite a target cell. Examples of neurotransmitters include dopamine, serotonin, q-aminobutyric acid, norepinephrine, histamine, acetylcholine, and epinephrine.

Cell response modifiers are chemotactic factors such as platelet-derived growth factor (PDGF). Other chemotactic factors include neutrophil-activating protein, monocyte chemoattractant protein, macrophage-inflammatory protein, platelet factor, platelet basic protein, vascular endothelial growth factor, and melanoma growth stimulating activity; epidermal growth factor, transforming growth factor (alpha), acidic and basic fibroblast growth factor, platelet-derived endothelial cell growth factor, insulin-like growth factor, nerve growth factor, and bone growth/cartilage-inducing factor (alpha and beta), or other bone morphogenetic protein.

Other cell response modifiers are the interleukins, interleukin inhibitors or interleukin receptors, including interleukin 1 through interleukin 10; interferons, including alpha, beta and gamma; hematopoietic factors, including erythropoietin, granulocyte colony stimulating factor, thrombopoietin, macrophage colony stimulating factor and granulocyte-macrophage colony stimulating factor; tumor necrosis factors, including alpha and beta; transforming growth factors (beta), including beta-1, beta-2, beta-3, inhibin, and activin; and bone morphogenetic proteins.

Antioxidants are substances which inhibit oxidation or suppress reactions promoted by oxygen or peroxides. Antioxidants, especially lipid-soluble antioxidants, can be absorbed into the cellular membrane to neutralize oxygen radicals and thereby protect the membrane. The antioxidants useful in the present invention may be selected from the group consisting of all forms of Vitamin A including retinal and 3,4-didehydroretinal, all forms of carotene such as Alpha-carotene, beta -carotene (beta, beta -carotene), gamma-carotene, delta-carotene, all forms of Vitamin C (D-ascorbic acid, L-aseorbic acid), all forms of tocopherol such as Vitamin E (Alpha-tocopherol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltri-decyl)-2H-1- benzopyran-6- ol), beta -tocopherol, gamma-tocopherol, delta-tocopherol, tocoquinone, tocotrienol, and Vitamin E esters which readily undergo hydrolysis to Vitamin E such as Vitamin E acetate and Vitamin E succinate, and pharmaceutically acceptable Vitamin E salts such as Vitamin E phosphate, prodrugs of Vitamin A, carotene, Vitamin C, and Vitamin E, pharmaceutically acceptable salts of Vitamin A, carotene, Vitamin C, and Vitamin E, and the like, and mixtures thereof.

When administered as flakes containing drugs, the formulations of the invention are applied in pharmaceutically acceptable amounts and in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, and benzene sulfonic. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

The active compounds of the present invention may be a pharmaceutical composition having a therapeutically effective amount optionally included in a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid or liquid filler, dilutants or encapsulating substances which are suitable for administration to a human or other animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions are capable of being commingled with the flakes of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

Compositions suitable for parenteral administration conveniently comprise a sterile preparation. This preparation may be formulated according to known methods. The sterile preparation thus may be a sterile solution or suspension in a non-toxic parenterally-acceptable diluent or solvent. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Carrier formulations suitable for oral, subcutaneous, intravenous, intramuscular, etc. can be found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA.

The conjugates of the invention are administered in effective amounts. An effective amount used in connection with a drug means that amount necessary to delay the onset of, inhibit the progression of, halt altogether the onset or progression of or diagnose the particular condition being treated. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Generally, daily oral doses of active compounds will be from about 0.01 mg/kg per day to 1000 mg/kg per day. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent patient tolerance permits.

Effective amounts of nondrug active agents, alone or in a single dose, or together with further doses, are those amounts accepted in the art as useful for administration to (including ingestion by) a subject. Such amounts in connection with vitamins, minerals, essential nutrients and herbal active agents are well known in the art.

A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, intravaginal, sublingual, topical, nasal, ocular, transdermal, intradermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous or intramuscular. Oral routes are preferred.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the conjugates of the invention into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as capsules, sachets, tablets, or lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion. One preferred capsule is shown in Fig. 2. The capsule 10 has mating-halves, 12 and 14. These halves are closed-end cylinders. Toward the closed end of each cylinder are gripping ridges 16 which allow the user to easily pull apart the two halves.

The microflakes also may be embedded in a tablet. The tablet can contain excipients that promote salivation, such as sugars that encourage swallowing by either salivation or lubrication (e.g. simethicone). This reduces the need for mastication of the tablet. The tablets may be fast dissolving. Excipients may be used which are solvents or gases, so that when the tablet is pressed and dried, the removal of the solvent or gas allows for the formation of open or closed cell-like structures within the tablet that hold the microflakes in place and dissolved rapidly in the moist environment of the oral cavity.

Examples

A. Rotating Drum Method

A drug solution containing acceptable pharmaceutical excipient is sprayed onto a rotating drum (roll drum drier). The rotary drum spray drier is operated by first turning on the turntable (1). This component requires a few minutes to reach the desired speed (e.g. 33 or 45 rpm). The spray head is then adjusted regarding position and the compressed air is fed to the spray head. The system is initially run with an air feed of approximately 1 L/min. with USP purified water feed of 25 mL/min. This operation is used to clean the system and observe the spray head action. Adjustments to the spray head position are made based on the water feed.

The water feed is next allowed to run dry and the system is dried using a radiant heating source. Once dry, the radiant heating source is turned off and the system allowed to cool to room temperature.

The system is used to produce flakes by next feeding solution into the spray head. The rate of feed and rotation rate of the rotor are adjusted to allow the feed solution to form a coat of the desired thickness on the rotor. This thickness preferably is less than 0.66 mm.

Also, the use of radiant heating and pulsing of the spray head, as well as the composition of the feed solution can be controlled to give a uflake of desired thickness.

Flakes are harvested from the rotating drum using the wiper blade. The flakes are collected on the turn table and removed using a vacuum recovery system.

The product is milled to form uniform flakes by mechanical milling. The preferred size range is 100-500 um.

The flakes are coated again to cover the edges and/or to add additional desired properties such as to provide a slip, taste masking or a moisture barrier or sustained or controlled release characteristic.

The drug flakes are reduced to the desired size (1 um to 5 mm) by a mechanical mill. The preferred range is 10-500 um.

The flakes are fractionated to the desired size distribution using mechanical screens or used as is.

The desired fractions are coated with a single or more coatings comprised of natural or synthetic polymers using a spray coater. The first coat can be comprised of methyl cellulose while the second can be a synthetic ionic polymer to impart selective solubility to the coating.

Example 1. Manufacturing of Diltiazem Drug Product:Immediate Release

The following components are used in the manufacture of immediate release diltiazem drug product.

Table 2. Component list for Excipients and Drug - Diltiazem immediate release

	Component	Range
1	600 g Diltiazem.HCl	25% in USP enthanol, 2.4 L
2	2.5 Kg Dextrose USP	255 solution in USP purified water, 10 L
3	3 g Carboxymethylcellulose	Solution of 3%, 100 mL

The rotary spray drier is turned on, washed and dried.

The components given in Table 2 are mixed until a homogenous solution is made.

This solution is fed into the rotor drum spray drier.

The radiant heater should be adjusted to give a drum temperature of about 45 C.

Under these conditions a thin film will be formed on the rotor head that will dry to a thin flake. The flakes are removed by adjusting the tension on the wiper arm.

Example 2. Additional manufacturing methods: Matrix based flakes

Matrix flakes can be manufactured through direct production as slurry through a heated drum roller system to give active flakes with sustained release characteristics.

Direct manufacturing through a drum roller is relatively simple, as opposed to the previous example of a spray drying method on a roller drum with scraper for flake removal. Acrylic polymer EUDRAGIT L 100-55 (3.5 Kg) and lactose (1 Kg) are added to the ingredients in Table 2 and suspended to give a relatively thick slurry. The mixture is kept suspended and fed into the trough leading into a heated roller drum assembly. The speed of the roller drum and temperature can be adjusted to allow generation of a thin ribbon, not exceeding 0.006 mm in thickness. The temperature is maintained below 60C.

The resulting ribbon is broken into large flakes and fed through an oscillating granulator to give a particle size of about 0.25 mm. This material is further sieved to give 0.1 to 0.55 mm diameter particles.

Example 3. Direct Coating on a Rotary Spray Drier for Sustained Release Product

Manufacturing of sustained release diltiazem flakes are achieved through either direct manufacturing of the rotary spray drier or after coating in a fluidized-bed process.

For direct generation of coated active flakes the solution given in Table 3 is first fed to the rotor head to coat the drum. Then the drug solution given in Table 2 is applied on top of this coating, followed by another layer of the solution of Table 3. This alternating spraying scheme is applied, then the wiper blade is applied and the coated active flakes are harvested.

A multi-spray head system can be used to apply multiple alternating layers of solutions given in Table 3 and 2, respectively, to allow continuous operation and harvesting of coated active flakes.

Example 4. Coating in a Fluidized Bed for Sustained Release Product

Coating of active flakes after manufacturing on the rotary drum spray dryer can be done using a conventional fluidized spray drier such as a Aeromatic Strea 1 (Niro Inc., Maryland, USA) or Glatt fluid-bed coater WSG 5 (Glatt Air Techniques Inc., New Jersey, USA)

For the fluidized bed coating the flakes can be sieved through a 0.55 mm diameter seive. The material manufactured from the components in Table 2 are coated with the components listed in Table 3, which represent a coating well known and used in the prior art to coat particles (which are not flakes).

Table 3. Component list for Sustained Release Excipients

	Components	Range
1	500 gm of 30% dispersion, EUDRAGIT RS 30 D	11.4% suspension
2	150 g Talc	11.4%
3	Triethyl citrate	2.3%
4	0.3 g Tween 80	0.02%
5	639.7 g USP purified water	74.88%

The uncoated flakes are placed in the fluidized drier and air is fed to the system. The solution from Table 3 is fed into the system in accordance with the manufacturer's instructions.

Upon conclusion, the coated flakes are dried and then placed on trays for airing.

Example 5. Coating of active flakes in a Top Spray Unit

Active flakes from Examples 1 or 2 can be coated using a top spray system such as a Glatt fluid-bed coater WSG 5 with an air gun and exhaust air screen. Flakes are placed in the unit and coated with components listed in Table 3. The system is operated in accordance with the manufacturer's instructions. After coating, the flakes are dried and then air dried on trays over night.

In another embodiment of the invention, the drug-incorporated flakes may be incorporated into a semi-solid base to form a spoon-able drug delivery system. The semi-solid base may be comprised of pectin, guar gum, xanthan gum, gum arabic, gum acacia, locust bean gum. carageenan gum, alginic acid, psyllium hydrocolloid, oat bran gum, rice bran gum, glucomannan, traganth gum, karaya gum, tapioca, corn starch, cellulose gums, agar, gelatin, polyacrylates, polysaccharides, polyvinylpyrolidones, pyrrolidones, polyols, collagen, polyethylene glycols, polyvinylalcohols, polyethers, polyesters, natural or synthetic oils, liquid paraffin, beeswax, silicon waves, natural or modified fatty acids, or combinations of thereof. Additionally viscous fruit purees such as apple, prune, apricot, pear, pineapple, banana, grape, strawberry, raspberry, blackberry, boysenberry, loganberry, dewberry, gooseberry, cranberry, mulberry, elderberry, blueberry, fig, currant, kiwi may be used.

In a preferred embodiment, the drug-incorporated flakes may be incorporated into the nutritionally fortified delivery vehicle (NFDV) of the invention to form a spoon-able drug delivery system with additional advantages of providing needed dietary requirements. See below for a more detailed discussion of the NFDV.

B. Roll Milling

Using acceptable pharmaceutical processing methods a drug substance is formulated and granulated.

The granules are compressed between a rolling mechanism including at least one deflection-compensating roller. Flakes are formed of a thickness of less than 0.1 mm.

The flakes are dried and processed as above.

C. Thin-film Manufacturing

Onto a moving belt is sprayed a thin film of coating agent such as ethyl cellulose. After drying a drug solution contained in a non-miscible solvent for the coating layer is sprayed. After drying a second layer of coating solution is sprayed to for a 3-laminated product.

The product is removed with a fixed knife blade and milled to form uniform flakes by mechanical milling. The preferred size range is 100-500 um.

The flakes are coated again to cover the edges and/or to add additional desired properties such as to provide a slip, taste masking or a moisture barrier or sustained or controlled release characteristic.

D. Spray, Inkjet or Drip Method

1. Inkjet, spray, or drip drug slurry onto belt dryer or barrel or flat surface drying device. This may be a continuous manufacturing process.

2. Drying can be effectuated by heat or vacuum or both.

3. In cases where drying is not necessary the slurry flakes may be polymerized, for instance, by infrared or ultraviolet radiation that does not degrade the drug product or other additives contained in the slurry.

4. In some cases both steps 2 and 3 may be used to manufacture the flakes.

5. In some cases, inert materials (e.g. gels, absorbents, etc.) may be used to create a flake and processed as described above. The flake may then be placed in contact with a drug so that it is absorbed. A subsequent drying or other step (e.g. polymerization) may be necessary to complete the formation of the flake.

6. Once produced the flakes may be coated with a variety of agents for taste masking, controlled drug release, enteric release or for other purposes known by those skilled in the art of drug dosage coatings. Multiple coating Coatings may incorporate compounds such as antistatic agents. Powders or other additives may be added to the flakes to promote the pouring of flow of the flakes from containers.

E. Press, Stamp or Embossing Method

1. Flakes may be produce by injecting or flowing a slurry into or onto a mold, cavity, a plurality of cavities or embossing a thin film of slurry in such a way as to form flake-like particles. This may be a continuous process.

2. Drying and/or polymerizing the flakes may be accomplished in a similar fashion as described above in Method 1.

F. Hybrid Methods

1. Flakes may be formed by plating or printing a nucleating agent onto a surface over which is flowed or exposed a saturated or supersaturated liquid. When the liquid comes into contact with the nucleating agent, small crystal-like flakes are formed. The process may be stopped by removal of the liquid, for instance. The flakes may then be coated or a subsequent crystal layer may be added of the same, or different agent.

2. Flakes may be formed by preparing a slurry which is photopolymerizable or contains a photopolymerizable agent in it. As a thin film of slurry passes by, it may be exposed to a polymerizing radiation source of controlled size so that flakes are formed *in situ*.

3. Flakes may be made out of a continuous sheet of woven or nonwoven material which is saturated with a drug and cut (e.g. laser, die cut, etc.) into small flat particles.

What is claimed is:

CLAIMS

1. A composition comprising:

a plurality of discrete, substantially flat flakes, each having an average length, an average width and an average thickness, wherein each of the length and width are at least three times the thickness, wherein a longest dimension of each flake is between 100 nanometers and 5 millimeters, and wherein the flakes comprise an agent selected from the group consisting of:

(a) an effective amount of a drug, and

(b) an effective amount of a nondrug active agent, provided that if the agent is only a nondrug active agent, then the nondrug active agent is selected from the group consisting of

(i) at least 1.0% by weight of the flakes of a noncalcium nondrug active agent selected from the group consisting of a vitamin and a mineral,

(ii) at least 3.0% by weight of the flakes of a nondrug active agent selected from the group consisting of a vitamin and a mineral, and

(iii) at least 3.0% by weight of the flakes of a nondrug active agent that is an essential nutrient,

(iv) at least 1.0% by weight of the flakes of an herbal bioactive agent combined with a binder and formed into the flakes, and

(v) a coated herb.

2. The composition of claim 1, wherein each flake has a surface area defined by multiplying the average length by the average width, and wherein the ratio of the surface area to the average thickness is selected from the group consisting of:

(a) at least 25 square units:1 unit, and

(b) at least 100 square units:1 unit.

3. The composition of claim 1, wherein the flakes further comprise a drug enhancing agent.

4. The composition of any one of claim 1, wherein the flakes are coated with a biocompatable coating which separates the agent from the environment otherwise surrounding the flake.

5. The composition of any one of claim 4, wherein the coating is selected from the group consisting of:

(a) an enteric coating,

(b) a taste masking coating,

(c) a pH sensitive coating,

(d) a temperature sensitive coating,

(e) a bioadhesive coating, and

(f) an extended-release coating.

6. The composition of claim 1, wherein the agent comprises a weight percent of the flakes selected from the group consisting of:

at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 12.5%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, and at least 50% of the flakes.

7. The composition of claim 1, wherein the agent is attached to the flake in a manner selected from the group consisting of:

(a) the agent is embedded in the flakes,

(b) the agent is coated on the flakes, and

(c) the agent is contained in microsheres attached to the flakes.

8. The composition of claim 1, wherein the flakes comprise at least two layers, each of the two layers being of a different composition.

9. The composition of claim 8, wherein the flakes comprise at least three layers.

10. The composition of claims 1, wherein the flakes comprise at least 20% by weight of a polymer selected from the group consisting of a natural polymer and a synthetic polymer.

11. The composition of claim 1, wherein the flakes comprise a nonfood, and the nonfood comprises a weight percent of the flakes selected from the group consisting of

at least 2.5%, at least 5%, at least 10%, at least 20%, and at least 25% by weight of the flakes.

12. The composition of claim 1, wherein the plurality of flakes comprises a mixture of two different types of flakes, a first type carrying a first agent and a second type carrying a second agent.

13. The composition of claim 1, wherein the agent is a drug and the drug is selected from the group consisting of: furosemide, digoxin; potassium chloride; divalproex; trazodone-HCl, ranitidine; phenytoin sodium, sertraline-HCl, risperidone, omeprazole; folic acid; haloperidol; nizatidine; carbamazepine; metoprotol tartrate; lisinopril; warfarin; cisapride; hydrochlorothiazide; nitroglycerin; methyldopa; carbidopa/levodopa; prazosin; oral hypoglyceremics; amantadine-HCl; hyoscyamine sulfate; fluoxetine; nifidipine; diltiazeim; phenotoxifyline; ketoprofen; aspirin; piroxicam; indomethacin; ibuprofen; isotretinoin; and triamtevene.

14. The composition of claim 1, wherein the agent is a drug and the drug is selected from the group consisting of: isotretinoin; oxazepain; lorazepam; piroxicam; loperamide; bromopheniramine; phenylpropanolanime; loratadine; famotidine; ordansetron; enalapril; captopril; phloroglucinol; nicergoline; acetaminophen; metapimazine; dihydroergotamine; fexofenadine-HCl and albuterol.

15. The composition of claim 1, wherein the agent is a plurality of drugs, and the plurality for drugs is selected from the group consisting of:

(a) furosemide and potassium chloride,
(b) metolazone and potassium chloride,
(c) Levadopa and carbadopa,
(d) Levadopa/carbodopa and docusate sodium/bisacodyl,
(e) tylenol/codeine and docusate sodium/disacodyl,
(f) tricyclic depressants and docusate sodium/bisacodyl,
(g) warfarin and nizatidine,
(h) amoxicillin and clavulanate, and
(i) imipenem and cilastatin.

16. The composition of claim 1, wherein the agent is selected from the group consisting of:

(a) Vitamin D and calcium,

(b) Vitamin D, calcium and magnesium,

(c) at least 10 vitamins and minerals, and

(d) Vitamin C, Vitamin E and Vitamin A.

17. A composition comprising:

a plurality of discrete, substantially flat flakes, each having an average length, an average width and an average thickness, wherein each of the length and width are at least three times the thickness, wherein a longest dimension of each flake is between 100 nanometers and 5 millimeters, and wherein each flake comprises a nonfood porous matrix.

18. The composition of claim 17 further comprising an agent contained in the porous matrix wherein the agent is selected from the group consisting of a drug, a vitamin, a mineral, an essential nutrient and an herbal active agent.

19. The composition of claim 18, wherein the agent is a drug.

20. The composition of claim 18, wherein the agent is a vitamin.

21. A pharmaceutical preparation comprising a unit dosage of the composition of any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, and 19, and optionally a pharmaceutically acceptable carrier, wherein the flakes are pharmaceutically acceptable, the agent is a drug and the drug is present in an amount effective for treating a human subject.

22. The pharmaceutical preparation of claim 21 formulated as an oral dosage form.

23. The pharmaceutical preparation of claim 21, wherein the pharmaceutically acceptable carrier is selected from the group consisting of a semi-solid and a hydrogel.

24. A method of treating a subject having a condition, with a drug, comprising:

administering to a subject in need of such treatment an amount of the drug effective to treat the condition, wherein the drug comprises a plurality of flakes.

25. The method of claim 24, wherein the flakes comprise the pharmaceutical preparation of claim 21.

26. The method of claim 24, wherein the flakes comprise the pharmaceutical preparation of claim 22.

27. The method of claim 24, wherein the flakes are administered orally.

28. The method of claim 24, wherein the subject is selected from the group consisting of a geriatric subject, a subject with cancer, a subject who is post-surgically recovering, a child and a pregnant mother.

29. In a method for preparing a pharmaceutical preparation by incorporating a drug within or coating a drug onto a particle, the improvement comprising incorporating the drug within or onto a flake.

30. The improvement of claim 29, wherein the flake comprises:

a plurality of discrete, substantially flat flakes, each having an average length, an average width and an average thickness, wherein each of the length and width are at least three times the thickness, wherein a longest dimension of each flake is between 100 nanometers and 5 millimeters.

31. A method for preparing a pharmaceutical preparation comprising incorporating a drug into or upon a plurality of flakes.

32. The method of claim 31, wherein the flake comprises:

a plurality of discrete, substantially flat flakes, each having an average length, an average width and an average thickness, wherein each of the length and width are at least three times the thickness, wherein a longest dimension of each flake is between 100 nanometers and 5 millimeters.

33. The method of claim 32, wherein the flakes are formed first, and then the drug is coated onto, or allowed to penetrate into, the flakes.

34. An article of manufacture comprising a capsule defining a chamber, and a plurality of discrete, substantially flat flakes, each having an average length, an average width and an average thickness, wherein each of the length and width are at least three times the thickness, wherein a longest dimension of each flake is between 100 nanometers and 5 millimeters wherein the flakes are contained within the chamber of the capsule.

35. The article of manufacture of claim 34 wherein the flakes comprise a drug.

36. the article of manufacture of claim 34, wherein the capsule is a pair of closed end mating cylinders, each of the pair provided with a nonsmooth gripping surface.

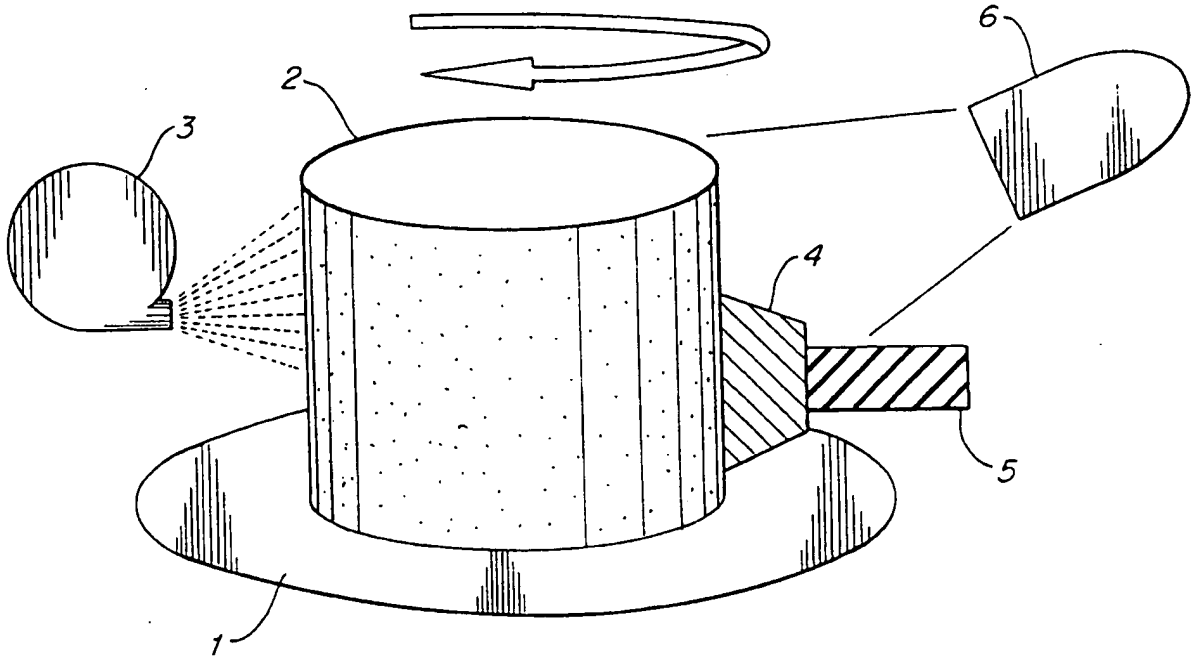

Fig. 1

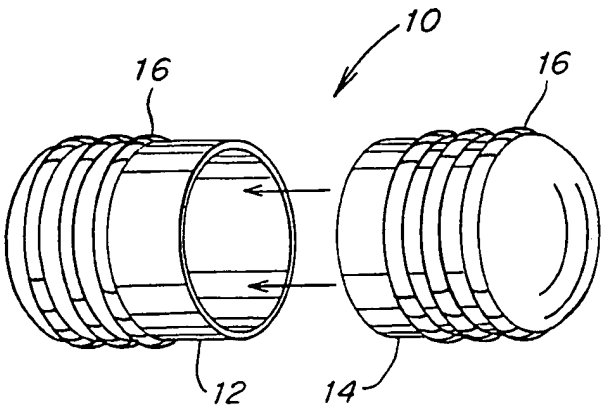

Fig. 2

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/US 98/26627

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 441 742 A (AUTANT PIERRE ET AL) 15 August 1995 ---	
A	GB 2 195 426 A (LE T I KHOLODILNOI PROM) 7 April 1988 -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 1999	21/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, W

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir... ...national application No.
PCT/US 98/26627

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 24-28
because they relate to subject matter not required to be searched by this Authority, namely:
See FURTHER INFORMATION SHEET PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 24-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims Nos.: 24-28

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 98/26627

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5441742 A	15-08-1995	FR 2703057 A	30-09-1994
		EP 0617074 A	28-09-1994
GB 2195426 A	07-04-1988	NONE	